PREDICTORS OF POST-STROKE FATIGUE

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I dedicate this dissertation to my father, a brave, relentless fighter who snickered at all the adversities that unpredictably occurred in his life: Thank you, for being the most influential man in my life. You are a scholar, a philosopher, a poet, a visionary, an avid tennis player, an outstanding speaker, and also a very demanding math teacher with abundance of discipline. More importantly, you are a survivor. You survived the poverty of being born in a fisherman's house with 8 children; you survived school teachers' belittling of your family's financial hardship; you survived Chiang Kai-Shek's "white horror" and Kuomintang's censorship in the name of national security; you survived cirrhosis; and you even survived a hemorrhagic stroke after a 10-day coma.

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Chapter 1

Introduction

1.1 Overview

In 2005, stroke was the cause for 5.7 million deaths worldwide and was identified as the second leading cause of death by the World Health Organization (WHO).[1] In the United States, stroke is considered as the most life-threatening neurological disorder and accounts for one of every fifteen deaths.[2] It has also been identified as the third leading cause of death and the first leading cause of disability in order adults.[3] Reports indicate that more than 780,000 new strokes occur each year in the United States.[4] Many survivors of stroke require extensive care,[5] and the health consequences of stroke have a substantial economic impact on not only the individual and family, but also on the society.[6]

Stroke can lead to loss of function both physically and cognitively,[7] and the severity of stroke dictates the severity of disablement. Depending on the lesion size and location, the injury to the brain can affect multiple systems.[8] These include motor and sensory impairments and language, perception, affective, and cognitive dysfunction.[9] Physical symptoms of stroke usually include weakness or paralysis. Most survivors of stroke show some residual loss of function on either the right or left side of the body, referred to as hemiplegia or hemiparesis.[10]

Secondary conditions in people post-stroke include a higher incidence of injury from falls, spasticity, memory loss, aphasia, sleep apnea, back pain, stress, and social isolation,[9, 11] while some of the common co-morbidities may include coronary heart disease, obesity, hypertension, type 2 diabetes, and hyperlipidemia.[12] In addition, it has been shown that up to 60% of people post-stroke can develop depression;[13] and there has been reported a high incidence rate of fatigue in people post-stroke as well.[11, 14-16]

Only recently, researchers have acknowledged the negative impact of post-stroke fatigue (PSF);[11, 17-19] and the causes of PSF appear multi-factorial.[20] However, PSF remains under-recognized and under-treated due to limited comprehensive investigation, although PSF is potentially a major public health concern. Therefore, the primary purpose of the present work was to differentiate unique types of PSF and determine its potential contributing factors. As a result of this work, we hope to obtain a better understanding in the nature of different kinds of fatigue in people with chronic stroke, and provide rehabilitation professionals adequate means to construct effective therapeutic treatments.

1.2 Stroke

Stroke is often referred to as a cerebrovascular accident (CVA). It is defined as a sudden, non-convulsive loss of neurologic function due to an ischemic or hemorrhagic intracranial vascular event[21] with rapidly developing clinical signs of focal or global disturbance of cerebral function. It can be mild with only short-term consequences or can cause severe long-term limitations in mobility and cognition.

Among all segments of the population, African-Americans have a greater risk of having a stroke than Caucasians or Hispanics and are more likely to be disabled from a stroke.[22] The likelihood of having the first stroke varies with sex and age.[9, 23] Men have a 30 percent greater risk of having a stroke than women in earlier life, while women have a greater risk in later life.[9] The risk of stroke increases approximately 5 percent per year in the 55-59-year-old age group. In the 80-84-year-old age group, the increased risk is approximately 25 percent a year thereafter.[23]

Stroke is considered a heterogeneous disorder because of its pathophysiology.[8] It can involve the rupturing of a large blood vessel in the brain,[8] also known as hemorrhagic stroke, which constitute approximately 10 percent of all strokes.[9] A hemorrhagic stroke results in blood leaking into the extravascular space within the cranium or into the brain tissue itself. Depending on where the injury occurs, hemorrhagic strokes can be classified as intra-cerebral (bleeding directly into the brain) or subarachnoid (bleeding into the spaces and spinal fluid around the brain). This bleeding damages the brain by cutting off connecting pathways and by causing localized or generalized pressure injury to brain tissue.[8]

Stroke can also involve the occlusion of a small blood vessel that affects a certain area of the brain,[8] also known as ischemic stroke, which makes up approximately 90 percent of all strokes.[9] It originates from a restricted blood supply, resulting in cell damage and impaired neurological function.[9] Ischemic strokes are divided into two types: thrombotic and embolic. Thrombosis refers to an obstruction of blood flow due to a localized occlusion within one or more blood vessels.[8] Thrombotic infarction occurs when a thrombus forms on an atherosclerotic plaque, while embolic infarction results when a material (embolus) is formed elsewhere and travels through the vascular system occludes an artery or arteriole in the brain.[24]

1.3 Fatigue

1.31 Historic View

Fatigue is one of the most common health complaints[25, 26] and is an important component of many physical diseases and psychiatric disorders.[27] It affects approximately 10-45% of community dwellers and patients who require primary care.[25, 28] Fatigue is a subjective feeling and is difficult to define. It can be represented either as a single phenomenon or a continuous event.[29]

Fatigue remains as difficult to measure as it was decades ago. Due to its ambiguous and subjective nature, researchers had proposed to banish the terminology and its related investigations from scientific discussion in the early 1920's.[30] Others decided to revisit this matter in the early 1940's.[31] After the late 1980's, more attempts have been made to investigate fatigue objectively and subjectively and theories started to emerge.[25, 29, 32-35]

1.32 Fatigue Redefined.

Literature suggests that fatigue is a complex and multidimensional phenomenon that can be defined from different perspectives.[32, 35-37] Since the perception of fatigue is subjective,[29] synonyms used to describe fatigue may be interpreted differently among individuals. For example, "feeling tired all the time" is more commonly used than "feeling weak."[38] This ambiguity makes the study of fatigue challenging. In the literature, many definitions of fatigue have emerged from different perspectives and disciplines.

In less restrictive terms, it is generally agreed to define fatigue as a subjective sensation of tiredness or lack of energy, and is experienced by most people at one time or another.[39] It has also been described as the inability to maintain the force or the production of force[40] and the inability to maintain sustained thought or mental ability.[41] In 1999, Aaronson and colleagues defined fatigue as the awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resource needed to perform activity.[37] In 2001, Staub and colleagues proposed that fatigue is defined as the feeling of early exhaustion, weariness, lack of energy and aversion to effort.[17] In 2004, the North American Nursing Diagnosis Association (NANDA) defined fatigue as an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work.[42]

All these definitions suggest that fatigue is determined by a person's subjective feeling about the state of one's internal resource and the nature of the activity being performed. However, the definition of global fatigue does not satisfy the view from other perspectives. For example, from the physiologic perspective, fatigue can be defined as reaching the maximal capacity of cardiopulmonary function[43] or maximal oxygen uptake (VO_{2max}), the product of maximal cardiac output and maximal arteriovenous oxygen difference as part of the oxidative metabolism process. On the other hand, fatigue can also be defined as a loss of maximal force-generating capacity during muscular activity, likely originates within muscle itself, and persists until muscle is fully recovered.[43] Piper and colleagues described fatigue as a multicausal, multidimensional sensation that affects sensory, affective, behavioral, and physiologic realms.[32] Using Piper's multidimensional view of fatigue as a conceptual framework, fatigue was defined as a sensation of depletion of internal resource, regardless of what nature or type of such resource may be in this dissertation project.

1.33 Fatigue Models.

The causes of fatigue remains debated. Nevertheless, several fatigue models have emerged since the 1980s. In 1989, Funk and colleagues proposed a neurophysiological model in an attempt to explain fatigue in terms of central and peripheral nervous system components.[33] They suggested that impairment of the central component leads to decreased motivation and transmission of messages from the brain and spinal cord. It also leads to exhaustion of brain cells in the hypothalamic region. Impairment of the peripheral component can change complex biochemical interactions between nerve and muscle that generate the force to movement.[33] Some researchers have described fatigue models from a physiological perspective.

In 1992, St. Pierre and colleagues demonstrated that physical symptoms of fatigue can be induced via alterations in metabolite concentration level.[44] Others have suggested a causal role of decreased aerobic capacity,[45] decreased muscle strength, endurance,[46] and increased oxygen consumption needs[47] to describe fatigue.

In addition, Bruno and colleagues proposed a viral damage model in 1993 to describe fatigue in patients with post-polio.[48] It was suggested that the effects of viral damage to the neurons of the reticular activating system impair the ability to maintain attention and leads to "brain fatigue," a symptom commonly experienced among survivors of polio described as a sensation of diminished concentration and drowsiness.

In 1987, Piper, Lindsay, and Dodd addressed the multidimensional nature of fatigue and suggested that the contributing factors of fatigue can be perceptual, physiological, biomechanical, and behavioral.[32] More specifically, Piper and colleague recognized the distinction between the objective dimensions (physiological, biomechanical, and behavioral) and the subjective dimension of fatigue (perception). In1989, Piper and colleagues further defined the subjective dimension of fatigue with 7 subdimensions (temporal, intensity, affective, sensory, evaluative, associated symptoms, and relief).[49] Figure 1.1 illustrates the conceptual framework of Piper's fatigue model developed based on cancer patients. It was believed that subjective dimension gives insight into how patients experience and better serves the research interest within the nursing science discipline.[50] Although the subjective subdimensions were abstract and less specific, Piper's view of fatigue suggests that fatigue cannot always be measured or explained objectively.

Based on the biochemical dimension described in Piper's fatigue model, Payne and colleagues investigated fatigue, sleep disturbances, and depressive symptoms in women with breast cancer by evaluating the changes in serum biomarkers levels during chemotherapy.[51] Payne's study included 11 women with stage II breast cancer receiving adjuvant chemotherapy and 11 people with no cancer as age-matched controls. Fatigue, sleep, and depressive symptoms were assessed by questionnaires, and serum samples were analyzed for biomarkers including serum cortisol, melatonin, serotonin, and bilirubin. The authors concluded that fatigue, sleep, and depressive symptoms are more prevalent in women with cancer than a cancer-free comparison group. In addition, it was suggested that serotonin, cortisol, and bilirubin can provide a possible explanatory mechanism for fatigue-related symptoms. This finding confirmed the theoretical framework based on the biochemical dimension of Piper's fatigue model; however, it does not address the multidimensional nature of fatigue as Payne's study only emphasized a singular dimension.

Piper's fatigue model also provided other researchers a theoretical framework to investigate the nature of fatigue. In 1999, Portenoy and colleagues conducted a review study and proposed an integrated fatigue model which consists of physiologic and psychosocial dimensions and several potential contributing factors.[52] Although based on cancer patients, Portenoy's integrated fatigue model was applicable to other clinical population such as people post-stroke due to several overlapping factors as illustrated in Figure 1.2. Consistent with Piper's view, this integrated fatigue model considers the multifactorial and multidimensional nature of fatigue, as recent studies have also suggested.[36, 37]

1.34 Fatigue Classifications.

Commonly, fatigue refers to a normal, everyday experience that most individuals report after exertion of physical power, inadequate sleep, or use of mental effort.[35] However, this definition does not distinguish the nature of different types of fatigue. Piper described a dichotomy fatigue concept,[53] which classifies fatigue as either acute or chronic, with duration of fatigue symptoms as the key discriminating factor as illustrated in Figure 1.3. This dichotomy fatigue concept is a broader interpretation of the original fatigue model[32] developed based on patients with cancer. It was proposed that other differentiating factors between acute and chronic are the onset of fatigue and the patient's recovery rate. To be specific, it was described that acute fatigue (Appendix I) has fast onset and quicker recovery.

It has been recently suggested that fatigue is not necessarily a symptom of disease but may be a daily experience of persons in the general population.[54] Consistent with Piper's dichotomy fatigue concept, researchers have distinguished this type of fatigue as "exertion fatigue (EF)" that is normative and is caused by extensive activities throughout daily living (Appendix I).[53, 55, 56] It is a state of general tiredness that is the result of over-exertion and can be recovered by rest. This type of fatigue is acute in nature, with a rapid onset and shorter duration.

On the other hand, "chronic fatigue (CF)" is differentiated from the normative types of fatigue and is associated with prolonged stress or pathologies(Appendix I).[53, 56] It is a state of weariness unrelated to previous exertion levels and is usually not alleviated by rest. This type of fatigue is chronic in nature with multiple possible causes, and is perceived to be abnormal or excessive. Unlike EF, CF may indicate a symptomatic condition of disease. In fact, CF is the symptom most frequently reported in the presence of many physical diseases, especially chronic ones such as cancer and multiple sclerosis.[25, 32, 33, 57] CF is also the key symptom of chronic fatigue syndrome (CFS), a condition which has gained much attention since the early 1990's.[25] The cause of CF is uncertain; but several factors may contribute to chronic fatigue such as depression, sleep disorders, medical treatment, and medications. More specifically, medical treatment for cancer such as radiotherapy or chemotherapy has been shown to induce chronic fatigue in patients.[32, 35, 57] Long-term usage of medications such as sleep agents also induces chronic fatigue.[35] In addition, it has been suggested that depression may be a key contributing factor to CF.[14, 58-60]

1.4 Fatigue Scales

1.41 Previous Fatigue Scales

Many attempts have been made in order to transform fatigue into a quantifiable measure.[27, 29, 34, 35, 50, 54, 55, 57, 61] To date, it is controversial to determine which fatigue scales are the most accurate and appropriate to assess PSF. Nevertheless, it has been suggested that the appropriateness of a fatigue scale should be determined by aspects of fatigue that are being measured.[62]

In 1989, Piper and colleagues developed the original Piper Fatigue Scale (PFS) to measure fatigue in cancer patients.[50] It consisted of 41 items along with visual analogue scale. However its length prevented it from becoming a practical research or clinical tool. In 1998, Piper and colleagues made an attempt to reduce the total number of items in PFS and to confirm the multidimensionality of the questionnaire.[57] It was a part of a larger mailed survey study conducted in urban and suburban areas in the northeast United States. More than 2,000 surveys were distributed to breast cancer survivors and 715 surveys (32%) were returned. Of all the respondents, 382 women met the study's criteria. The revised version consists of 22 questions divided into four subscales that measure behavioral/severity (6 items), affective meaning (5 items), sensory (5 items) and cognitive/mood (6 items). Despite the multidimensional approach of the revised PFS, the results revealed redundancy of the scale and further revision was suggested.

Chalder et al. in 1993 developed the Chalder Fatigue Scale (CFS) to measure the severity of fatigue.[29] It consists of 14 questions which measure mental and physical symptoms of fatigue. Three hundred and forty-seven subjects between the ages of 18 and 45 were asked to complete the test in a clinical setting in England. The results revealed a high degree of internal consistency for all items (Cronback's alpha 0.88 - 0.90). In addition, the original 14 items were placed into two different factors to describe physical (items 1-8) and mental (item 9-14) fatigue. In 1998, Morriss and colleagues revisited the validity of the CFS in 136 patients with chronic fatigue syndrome.[63] The original 14 items were categorized into 4 factors – cognitive difficulties, tiredness and sleepiness, strength and endurance, and loss of interest and motivation, which accounted for 67.1% of total variance in the scores on the fatigue scale. Their results agreed with Chalder et al and demonstrated validity of the scale.

However, some items in the CFS were significantly associated with more than one factor and can be interpreted differently. For example, the item "problems starting things" was associated with both Factor 1 - cognitive difficulties (factor loading index = 0.49) and Factor 4 - loss of interest and motivation (0.46); and the item "lacking energy" was associated with both Factor 2 - tiredness and sleepiness (0.69) and Factor 3 - strength and endurance (0.42). Such items make distinction between EF and CF difficult; therefore CFS was not considered in this project.

Other researchers also attempted to measure the multidimensional aspect of fatigue. In 1995, Smets and colleagues developed a five-dimensional fatigue scale that did not intend to contain any confounding somatic items.[35] The Multidimensional Fatigue Inventory (MFI-20) consists of 20 items divided into five subscales with a visual 5-point Likert scale. The five subscales include general, physical, mental fatigue, reduction in activity, and reduction in motivation; and each subscale yields four items. The questionnaire was tested for its psychometric properties in cancer patients receiving radiotherapy (n=111), patients with the chronic fatigue syndrome (n=357), psychology students (n=481), medical students (n=158), army recruits (n=160 & 156) and junior physicians (n=46). The results showed validity of the MFI-20 with an internal consistency (Cronbach's alpha = .84). Construct validity was established after comparisons between and within groups, and convergent validity was investigated by correlating the MFI-scales with a Visual Analogue Scale measuring fatigue ($0.22 < r < 0.78$). However, a later study by Schneider only partially supports the MFI-20.[61] In Schneider's study, the same MFI-

20 scale was administered to 97 cancer patients to replicate internal consistency and reliabilities of the MFI-20. The results showed that three of the five subscales from the MFI-20 reported moderate to low internal consistency (Cronbach's alpha = 0.43 - 0.64); and the author suggested using the General Fatigue subscale as a global indicator to represent fatigue. Despite the high internal consistency (Cronbach's alpha of 0.74) found in the General Fatigue subscale, it only yields 4 items and may not be well-constructed enough to detect fatigue. In addition, some items in the MFI-20 are related to either behavioral or psychosocial consequences which may be confounding.

Michielsen et al. in 2003 proposed a 10-item Fatigue Assessment Scale (FAS) that measures psychometric qualities of fatigue in 351 people with a minimum of 20 working hours per week.[27] Out of the 10 items composing the FAS, 1 item was novel and 9 were selected from an item pool consisting 40 items taken from other commonly used fatigue questionnaires. The results showed an internal consistency of 0.90. However, this questionnaire is fundamentally unidimensional and was conducted in a non-pathological population. The test-retest reliability and the validity may be questionable in specific clinical population such as people post-stroke.

1.42 Measuring Chronic Fatigue

Among all existing fatigue scales, one particular scale appears to adequately identify and measure CF. In 1989, Krupp and colleagues developed a nine-item Fatigue Severity Scale (FSS) for subjects with multiple sclerosis and with systemic lupus erythematosus to compare fatigue in two chronic conditions.[34] The FSS measured level of fatigue in the previous 2-weeks and was administered with a 7-point Likert scale to 25 subjects with multiple sclerosis, 29 subjects with systemic lupus erythematosus, and 20 healthy adults. The results revealed that the FSS was internally consistent. It also showed that fatigue had a greater impact on daily living in patients with multiple sclerosis and systemic lupus erythematosus than controls; while fatigue can exist independently of depressive symptoms. Krupp and colleagues demonstrated a clinically feasible method to identify the features that distinguish CF using the FSS.

In 2006, a study by Schepers and colleagues[64] examined the relation between fatigue at 1 year post-stroke and personal characteristics, stroke characteristics, and post-stroke impairments. One hundred and sixty-seven people post-stroke were included in this study via inpatient rehabilitation programs from 4 Dutch rehabilitation centers. The FSS was administered to measure fatigue at 3 different time points – initial admittance for inpatient rehabilitation, 6 months, and 1 year post-stroke. The results demonstrated intraclass correlation coefficient (ICC) of 0.82 and internal consistency (Cronbach's alpha of 0.89) in people post-stroke.

The FSS emphasizes the impact of fatigue on daily life in terms of accumulation of functional fatigue effects, which appears suitable for detecting the presence and the severity of CF. Furthermore, the FSS has been recently used to measure fatigue in several PSF studies.[11, 16, 64-66] In this dissertation project, the FSS was used as one of the measures to assess CF in people post-stroke.

1.43 Measuring Exertion Fatigue

Since EF is a relatively overshadowed concept due to the prevalence of CF in many clinical populations, very few investigators have attempted to develop a quantifiable scale to measure EF. In 1998, Tiesinga and colleagues proposed that the Dutch Exertion Fatigue Scale (DEFS) can be used to assess EF in patients with heart disease, postpartum women, and patients living in a home for the elderly.[55] Although they attempted to differentiate EF from generic fatigue, the DEFS has not been validated in people with chronic stroke.

In 2005, Yang et al proposed the Situational Fatigue Scale (SFS) that specifies the nature and the duration of daily activities in which subjects estimate their level of fatigue subjectively.[54] They suggested that most fatigue scales allow subjects to rate their level of fatigue without specifying the situation. Yang and colleagues further argued that the level of fatigue is determined not only by the availability of inner resources but also by the demands of the activities performed, therefore duration and type of activity must be specified when measuring fatigue. The SFS was administered as a survey to 96 outpatients in a family-medicine clinic and to 63 college students. The results revealed internal consistency and test-retest reliability and suggested that the SFS could be a useful tool to measure the broad concept of fatigue. However, many items in the SFS were too specific to the types of activity involved and may not be applicable to clinical population with physical limitations.

In 2006, Smith and colleagues conducted a pilot study to look at changes before and after a single bout of exercise in 34 people with multiple sclerosis.[67] They collected data in function, fatigue, and sensory symptoms before exercise, immediately after exercise, and 24 hours later. Subjects were asked to exercise between 5 to 45 minutes (mean = 17.4 min) at an individually prescribed intensity of 7 to 17 (median = 12) on the Borg's Rating of Perceived Exertion (RPE) scale.[68, 69] It is important to acknowledge that the RPE reflects the perceived level of exertion during exercise, not the level of fatigue after exercise. In addition, Smith and colleagues used a self-reported visual analog scale with score ranges from 1 to 100 to measure the intensity of fatigue.[67] All outcome measures were self-rated by subjects. Although no significance was found in fatigue levels between pre-exercise, immediately post-exercise and 24 hours post-exercise, Smith and colleagues provided methodological groundwork to measure EF in clinical populations. Furthermore, the visual analog scale has been used in recent studies to investigate fatigue in people post-stroke.[16, 65, 70] In this body of work, a similar visual analog scale was developed specifically for people post-stroke and was used to detect fatigue with different natures.

Despite all previous efforts to investigate fatigue with various approaches, not many scales were designed to differentiate EF from CF; and all existing fatigue scales lack objective measurement to validate the presence of fatigue with physiologic responses and changes. This dissertation project attempted to address these issues by 1) developing a clinically feasible scale that could detect either EF or CF each with its unique assessment method, and 2) validating the scale with physiologic response and changes during exercise testing.

1.5 Post-Stroke Fatigue

Post-stroke fatigue (PSF) is a prevalent symptom among survivors of stroke,[11, 14-17, 20, 71, 72] with an incidence rate as high as nearly 70%.[11, 64] However, it is a commonly neglected issue by clinicians as well as care-givers.[11, 14-17]

In an earlier PSF study, Ingles and colleagues[11] conducted a survey study in a community setting in order to investigate the frequency and outcome of fatigue, its impact on functioning, and its relationship with depression in people post-stroke. They administered a self-report questionnaire known as the Fatigue Impact Scale (FIS)[73] to 181 people post-stroke. The FIS measures the presence and severity of fatigue and its impact on cognitive, physical, and psychosocial functions. In addition, a Geriatric Depression Scale (GSD)[74] was also administered to detect depressive symptoms. To meet the inclusion criteria, the participants must have a cerebral infarct or an intracerebral hemorrhage and was discharged from the hospital. They were excluded from the study if (1) they had experienced another stroke after admission of study; (2) abused alcohol or had another neurologic disease; (3) did not speak English; or (4) they were unable to answer questions or complete self-rating questionnaires due to cognitive impairment. Eighty-eight participants (33 women, 55 men) ranged from 27 to 91 years of age (mean = 66.6, SD = 13.4) between 3 and 13 months post-stroke (mean = 212 days, SD = 85.3) met the criteria. The control group consisted of 56 elderly participants (38 women, 18 men) ranged from 62 to 93 years of age (mean = 73.9, SD = 7.9). They were excluded if they had a history of stroke, neurologic disease, or alcohol abuse. The results found that 68% of 88 people reported fatigue problems, greater than the control group (36%, $p < .001$); 40% percent of the stroke group reported that fatigue was among their worst symptom. Surprisingly, fatigue was not found related to time post-stroke, stroke severity, or lesion location. Although the presence of fatigue was independent of depression, the authors concluded that fatigue can contribute to functional impairment even long after the onset of stroke (i.e. 13 months) and suggested that the treatment to post-stroke fatigue is important for stroke recovery.

In 2001, Van der Werf and colleagues conducted a survey study by mail in people with at least 1 year of time post-stroke.[14] The purpose of this study was to test whether fatigue persists long after a stroke has occurred, and to assess the relation between fatigue and levels of physical impairment and depression. One hundred and thirty-eight participants were mailed the questionnaire and were asked to find an age-match control without previous history of stroke to fill out an additional questionnaire. Sixty-five percent of the stroke group and 37% of the control group responded. In this study, fatigue was measured using the Checklist Individual Strength (CIS),[75] a 20-item self-report questionnaire that quantifies subjective fatigue and related behavioral aspects; while the functional disability was measured by Sickness Impact Scale (SIP) consists of 7 subscales.[76] The results showed that 50% of people post-stroke experienced fatigue as their main complaint, significantly more frequent than the 16% in the control group. There was a significant difference in functional impairment between groups and no significant difference was found in depression. Consistent with Ingle and colleague's findings in 1999, Van der Werf et al. suggested that fatigue can persist long after stroke. They also found that physical impairment and depression were related to levels of fatigue but were not related to time post-stroke. In addition, walking impairment explained most of the variance in the stroke group.

In 2002, Glader et al. collected responses from people approximately 30 months post-stroke to investigate post-stroke fatigue in Sweden.[15] The purpose of this large study was to determine the prevalence of fatigue independent of depression in people post-stroke and the impact fatigue on different aspects of daily life. Of the 8194 patients registered in a hospital-based national stroke register, 5189 lived past 2 years after stroke and 4023 (77.5%) responded a mail questionnaire. In this study, individuals who reported persistent depressive symptoms were excluded. The results revealed that of the 3667 stroke survivors who returned the questionnaire and met the criteria, 39.2% reported moderate to severe fatigue in spite of the absence of depressive symptoms. Three years after stroke, patients with fatigue also had a higher fatality rate than those without (17.3% versus 7.1%, $p < .001$). Glader and colleagues concluded that fatigue is frequent and can be severe even late after stroke, which is consistent with previous findings.[11, 14] The authors also pointed out that PSF usually receives little attention by healthcare professionals and intervention studies were suggested.

In 2005, a study of Korea evaluated the characteristics of and the factors associated with PSF.[16] Via mail-surveys, Choi-Kwan and colleagues studied 220 outpatients at an average of 15 months after the onset of stroke. The presence of PSF was assessed using the Fatigue Severity Scale (FSS)[34] and the impact of post-stroke fatigue on patients' daily activities was also measured using Fatigue Impact Scale (FIS).[73] In addition, presence of post-stroke depression and post-stroke emotional incontinence were also identified with questionnaire. The results reported that 57% of 220 people 15 months post-stroke had fatigue problems and 24% had post-stroke depression. In addition, 50% of the people without post-stroke depression also post-stroke fatigue. Like previously suggested,[11, 14, 15] Choi-Kwan and colleagues also concluded that fatigue is a common complaint among people post-stroke, and it can be independent of depression.

1.6 Contributing Factors to PSF

1.61 Overview of Potential Factors

In 2003, de Groot and colleagues conducted a comprehensive literature review to address PSF.[20] They examined the phenomenon of fatigue in stroke and other neurologic disorders and suggested treatment strategies by reviewing the occurrence, frequency, duration, severity, and associated factors of fatigue. de Groot and colleagues evaluated the purpose, design, and conclusions from over 1000 articles to determine the validity and relevance to the topic of PSF. Their findings highlighted numerous potential contributing factors specific to PSF. Similar to Portenoy's integrated fatigue model,[52] this model consists of physiologic and psychologic factors as two distinct dimensions as illustrated in Figure 1.4. Physiologic factors include immobility or inactivity, biochemical abnormalities, systemic disorders, medication side effects, sleep disorders, and altered nutritional status; psychological factors include comorbid mood disorders, increase of perceived effort, and illness related stressors. Specifically, physiologic factors that are commonly experienced in people post-stroke such as physical deconditioning and physical impairment are listed as potential contributors to PSF; while another prevalent post-stroke comorbidity – depression, is included as a potential psychological contributing factor. These findings help to identify the parameter of potential contributing factors specific to PSF. In this body of work, we examined three variables that are considered substantial contributors to PSF - aerobic fitness,[10, 77, 78] physical impairment,[14, 15, 65] and depression.[11, 14-16]

1.62 Aerobic Fitness

People post-stroke have diminished aerobic fitness.[10, 45, 77, 79] Previous studies have assessed the peak oxygen uptake (VO_{2peak}) of stroke survivors[77, 79] and reported low peak VO_2 levels (13 ml/kg/min ~ 16 ml/kg/min) among people post-stroke, which is only 50% of healthy older adults. A comparable reduction was reported in maximal walking velocity (1.02+/-0.28m/s) and endurance (294.1+/-120.2m) by conducting a six-minute-walk test.[78, 80] This reduced VO_{2peak} may be attributed to a reduction in the number of motor units capable of being recruited during dynamic exercise, the reduced oxidative capacity of paretic muscle,[81] and the sedentary lifestyle of most stroke survivors.[79]

In 2006, Michael and colleagues investigated how aerobic fitness, mobility deficit, ambulatory activity, self-efficacy for falls, and social support are related to fatigue in 53 people post-stroke.[65] The severity of fatigue was examined using Fatigue Severity Scale (FSS)[34] and the Visual Analog Scale (VAS);[82] aerobic fitness was assessed at the peak level using a graded exercise protocol on a treadmill. In addition, timed 10-meter walks, the Berg Balance Scale, total daily step activity, the Medical Outcomes Study Social Support Survey, and the Falls Efficacy Scale were also administered. They found that 46% of people post-stroke had severe fatigue; fatigue showed an inverse relationship with falls efficacy and social support, but not with aerobic fitness or ambulatory activity. Although their finding did not show a direct association between aerobic fitness level and PSF, aerobic exercise has been shown to increase aerobic fitness after stroke,[77, 78] and its effects on PSF is a subject worthy of study. In this study, VO_{2peak} was assessed as a potential predictor of PSF using a maximal effort graded exercise test on a total body recumbent stepper.[83]

1.63 Physical Impairment

Physical impairment is considered a contributing factor to PSF due to some limitations in people post-stroke, such as decreased strength, limited range of motion, muscle tone, mal-alignment, abnormal synergy, and poor coordination, which lead to poor biomechanical efficiency. Specifically, people post-stroke often experience the increased energy expenditure of hemiparetic gait due to the inability to activate normal motor patterns.[84]

To investigate the physical impairment issues, Pohl and colleagues evaluated the walking performance in people post-stroke.[85] Seventy-two people with chronic stroke were asked to complete the 6-minute walk test (6MWT); pulse and blood pressure were taken before and after the walk. Motor control ability was measured by the Fugl-Meyer lower extremity (FMLE) motor score; balance was measured by the Berg Balance scale (BBS). Using regression analysis, the authors found that the FMLE and BBS explained 45 percent of the variance in distance walked and concluded that stroke-related neuromuscular impairments contribute to diminished performance in the 6-minute walk test. As confirmed in later research,[86] people post-stroke show changes in the motor control strategies as demonstrated in abnormal muscle activation patterns.

More interestingly, researchers have found that in people post-stroke, even extremities of the less-affected side demonstrate weakness and incoordiantion,[87-89] which may be a contributing factor for fatigue. In 2003, Kim and colleagues examined targeted movements in both the ipsilateral and the contralateral extremities in people post-stroke.[89] Ten right-handed individuals who were more than 6 months post-stroke with Fugl-Meyer motor assessment scores greater than 75% participated in this study. In addition, 20 age-matched adults without stroke comprised the control group for comparison. The outcome measures included movement time and dwell time of hand or foot. The results revealed that regardless of target size, movement and dwell times for both upper extremities of the stroke group were prolonged compared with those without stroke; while dwell time for both lower extremities of the stroke group was also longer than the control group. The authors then concluded that although subtle, the ipsilateral extremities may show motor control deficits after stroke. This finding invites the investigation to determine whether or not physical impairment contributes to fatigue in people post-stroke.

Some researchers have measured muscular strength in order to describe PSF.[90, 91] In 2007, Hidler et al conducted an electromyography (EMG) study to examine the diminished strength and abnormal synergy patterns in people post-stroke.[91] Ten people post-stroke and nine age-match controls participated in the study. EMG was used to recorded muscle activations during maximum isometric contractions in a standing position. In addition, joint torques at the knee and hip were measured. Their results indicate that stroke subjects demonstrated significantly lower maximum isometric torque than age-matched control subjects. The EMG data also indicate that the stroke group subjects activated antagonistic muscle groups significantly higher than the control group. The authors concluded that poor volitional torque generating capacity is a primary contributor to lower limb motor impairment in acute hemiparetic stroke.

Although dynamometer and EMG provide direct measurement of force output and muscle activation, respectively, muscular strength does not reflect the motor control issue commonly experienced in people post-stroke in order to describe PSF.[92] In 1999, Svantesson and colleagues examined muscular fatigue in people post-stroke in order to investigate mechanisms behind fatigue affected by stroke. Subjects were asked to perform repetitive eccentric-concentric plantar flexions on a dynamometer until exhaustion. The mean power frequency and root mean square of the EMG were recorded. However, the results did not report any significant differences in number of repetition performed or work between any of the tested legs in the stroke group. The authors concluded that in people post-stroke there may be other peripheral fatigue factors not reflected in the EMG activity.

In this dissertation project, motor control was assessed as a potential predictor of PSF. The assessment was conducted using the Fugl-Meyer (FM) test.[93] The FM was specifically designed as a clinical measure of sensorimotor impairment for stroke;[93] it has been shown to be a reliable and valid tool to assess level of motor control in people post-stroke.[80, 85, 94] Furthermore, several researchers have used FM as an indicator of stroke severity or impairment.[95-97] In this study the level of motor control was reflected by the FM total motor score (FMTM), which consisted of the combined scores from the upper extremity (UE) and the lower extremity (LE) portions of the FM test.

1.64 Depression

Depression is commonly associated with fatigue; and the close relationship between depression and fatigue has been recognized in people with multiple sclerosis,[98-100] epilepsy,[101] systemic lupus erythematosus,[102] and HIV.[103] In addition, depression is also associated with other psychiatric disorders such as increased risk for suicide and treatment resistance,[104] with adds to the severity of its comorbidities.

Like people post-stroke, patient with multiple sclerosis (MS) also experiences fatigue.[34] Depression is a prevalent issue in people with MS; and it affects as many as 60% of patients.[99, 105] In a study that investigated the impact of fatigue and depression on quality of life (QOL) in people with MS,[58] Janardhan et al examined studied 60 patients with MS. QOL was assessed using Multiple Sclerosis Quality of Life (MSQOL)-54; fatigue was assessed using the Fatigue Severity Scale (FSS); and depression was measured using the Hamilton Depression Inventory. The results indicate that fatigue and depression are significantly associated with lower QOL scores; and both fatigue and depression are independent predictors of impaired QOL in patients with MS. The authors concluded that recognition of fatigue and depression is important for effective treatment to improve QOL in patients with MS.

In people post-stroke, depression is the only identified factor with a significant relation to PSF.[14, 59, 106] Nevertheless, fatigue is frequent and can persist late after stroke;[15] more interestingly, it can exist independently of depression[11, 14-16] In 1999, Ingles and colleagues conducted a survey study to study PSF and its relationship with depression in people post-stroke.[11] They administered the self-reported Fatigue Impact Scale (FIS) that measures the presence and severity of fatigue and its impact on cognitive, physical, and psychosocial functions to 181 people post-stroke. In addition, they also administered the Geriatric Depression Scale (GDS) to measure the severity of depressive symptoms as did in our study. Out of the 88 participants who met the criteria and participated, they found that 68% of participants reported fatigue problems, while 40% of which were depressed. This finding revealed the prevalence of depression in people post-stroke.

In addition, a Korean study in 2005 evaluated the characteristics of and the factors associated with PSF in 220 people post-stroke.[16] Choi-Kwan and colleagues reported that 57% of 220 people 15 months post-stroke had fatigue problems and 24% had depression. In addition, 50% of the people without depression also had PSF complaint. Consistent with Ingle's finding, they found the prevalence of fatigue among people post-stroke. In addition, it was also suggested that fatigue can exist independently of depression.

Previously researched has suggested that depression should be considered when investigating PSF[66] while acknowledging other factors may also play a role as a contributor.[64] In this dissertation study, depression was examined as an important determinant of PSF using the Geriatric Depression Scale (GDS).[74]

1.65 Lesion Characteristics

In people post-stroke, the relationship between the presence of fatigue and stroke subtype and lesion location has been controversial. Recent neurobehavioral studies suggested that fatigue may be linked to the interruption of neural networks.[17] In contrast, some researchers proposed that stroke subtype or lesion side did not seem to be related to PSF.[11, 15, 16]

In 1995, Sisson examined the relationship between emotional, behavioral and cognitive status and functional activity status in people post-stroke.[107] Fifteen right hemisphere stroke survivors were included in this study. Their finding suggests a relationship between right-hemispheric strokes and fatigue or lack of energy.[107] It has been hypothesized that the subjective feeling of lack of energy is a result of disconnection between the right insula and the frontal lobe.[108]

In a in 2001 study, Staub and colleagues[17] found that fatigue was found mainly in people with a brainstem infarct at 54.5%, less often in people with subcortical infarct at 37.5%, and rarely in people with cortical infarct at 6.25%. However, no significant correlation was found between fatigue and stroke severity, lesion location, cognitive and neurological impairment and depression. Despite the results, the authors proposed that PSF may be linked to attentional deficits resulting from specific damage to the reticular formation and related structures involved in the subcortical attentional network. It was also suggested that fatigue may develop after stroke in connection with cognitive sequelae, neurological impairment, psychological factors and sleep disorders.

On the contrary, some researchers have suggested that stroke subtype and lesion side or location did not seem to be related to post-stroke fatigue.[11, 14-16, 64] In a survey study by Ingles et al., the frequency and outcome of fatigue, its impact on functioning, and its relationship with depression in people post-stroke was investigated.[11] The results of this study demonstrated that fatigue is not related to lesion side and location. Glader et al. also found no association between fatigue and stroke subtype but hypothesized that PSF may be a result from a combination of a brain lesion and inappropriate coping with a new life situation after the stroke.[15] In

2006, Schepers and colleagues examined the relation between fatigue at 1 year post-stroke and personal characteristics, stroke characteristics, and post-stroke impairments.[64] The results revealed consistent finding as previous studies[11, 15] to support that fatigue is not related to lesion side and stroke location.

Because of the contradicting findings from previous investigations, the relationship between the presence of fatigue and stroke lesion side and location is unclear. This dissertation project documented subjects' lesion side (left versus right) and stroke subtypes (ischemic versus hemorrhagic) and included them in the analysis as secondary factors.

1.66 Sleep Disorders

Sleeping problems have been reported in people post-stroke frequently due to sleep-related breathing disorders.[109] In 2000, Parra and colleagues investigated the prevalence and behavior of sleep-related breathing disorders (SRBDs) associated with stroke or transient ischemic attack (TIA). One hundred and sixty-one people post-stroke in the acute phase were admitted in this study and underwent complete neurological assessment. In this study, stroke subtype was categorized as TIA, ischemic (IS), or hemorrhagic (HS). A portable respiratory recording (PRR) study was performed in the acute phase within 48-72 hour after admission and stable phase after 3 months. During the acute phase, 116 patients (71.4%) had an apnea-hypopnea index (AHI) > 10 events/h and 45 (28%) had an AHI > 30. No relationships were found between sleep-related respiratory events and the lesion location. Cheyne-

Stokes breathing (CSB) was observed in 42 cases (26.1%). There were no significant differences in SRBD according to the stroke subtype. A second PRR was performed during the stable phase in 86 participants: 53 of 86 (61.6%) had an AHI > 10 and 17 of 86 (19.7%) had an AHI > 30. The AHI in the stable phase was significantly lower than the acute phase while the obstructive apnea index (OAI) remained unchanged. CSB was observed in 6 of 86 patients. These results demonstrated the prevalence of SRBD in people with first stroke. Even though no correlation was found between neurological location and the presence or type of SRBD, it is undeniable that SRBD can impact the quality of sleep and indirectly contribute to fatigue. Furthermore, Van der Werf and colleagues hypothesized that certain sleep-related breathing problems are related to PSF.[14] A relation between sleep disorders and PSF is likely to exist due to the quality of sleep or oxygen deprivation, which merits further exploration. In this dissertation project, documentation of sleep apnea was included as a secondary factor.

1.67 Medication Side Effects

A number of medications commonly used in people post-stroke such as β-blockers, hypnotics, antihypertensives, antihistamines, anticonvulsants, corticosteroids, and opiates may lead to fatigue due to side effects.[110]

An early study by Dimsdale and Newton examined the effects of atenolol and metoprolol on neuropsychologic functioning, mood, sedation, and sleep. This double-blinded study included 35 people with hypertension who randomly received either atenolol or metoprolol for 4 weeks. The results did not reveal any significant changes in mood, sedation, or deep sleep as a consequence of treatment with a beta blocker; however, there was a trend for a poorer mood profile in subjects who received metoprolol. More importantly, subjects on both medications had substantial complaints of fatigue.

In a recent study to evaluate the relationship between the use of sleep agents and quality of life (QOL) in people with cancer,[111] 909 oncology patients were interviewed in clinic setting at three different hospitals. QOL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and compared between sleep agent users vs. non-users. Paltiel and colleagues found that 25.7% of subjects use sleeping pill; in addition, they found a significant increase of fatigue severity comparing to non-users. The authors concluded that the use of sleep agents was associated with substantially poorer QOL and increased severity of symptoms.

Because sleep agents may be commonly prescribed among people post-stroke with sleep disorders, it was included in analysis as a secondary factor. In addition, although antidepressants are commonly prescribed among people post-stroke, depressive symptoms can still persist under prescription of antidepressants.[104] Antidepressant usage was also included in analysis as a secondary factor in this study.

1.7 Distinction of Experimental Design

1.71 Visual Analog Fatigue Scale

Previous studies used the generic horizontal version of the visual analog scale to measure fatigue.[16, 65, 70] However, the validity of data may be questionable due to visual field defect, neglect or other visual-perceptual deficits commonly experienced among people following stroke. We developed the Visual Analog Fatigue Scale (VAFS) as a vertical scale to assess PSF in order to eliminate subject difficulties and poor data validity. The VAFS is modified from a previously validated vertical version of visual analog scale that was designed to assess sleep-related breathing disorders in people post-stroke.[109]

1.72 Real-Time Fatigue Assessment

Previous studies used the original visual analog scale to measure fatigue over a certain time period (e.g. previous 2 weeks),[16, 65, 70] This assessment method does not allow the scale to be sensitive to EF. In this dissertation project, the VAFS was used to assess the level of fatigue before and after exercise; EF was then calculated the as difference between fatigue levels pre-exercise and immediately post-exercise. This approach allowed the truthful reflection of EF that was exclusively induced by exercise. In addition, we were able to utilize the VAFS to detect fatigue level at-rest, which indicated the type of fatigue that is persistent and chronic in nature. This real-time assessment method to detect CF was unique from conventional questionnaire-based fatigue scales that require subject's recollection of previous events that could have higher subjectivity and variance.

1.8 Significance of the Presented Work

PSF is a complex phenomenon, and it has been stressed that PSF should be recognized, evaluated, monitored, documented, and treated at all stages.[18] However, conclusive evidence on determinants of PSF is still limited regardless of the previous effort. Very few studies have examined how the potential contributing factors relate to PSF using quantifiable outcome measures, and no study has yet to investigate PSF by distinguishing EF from CF using outcome measures as potential predictors. Difference in the instruments used and the lack of objective physiologic measurements of fatigue make it difficult to compare findings measuring fatigue. It is essential to invest more effort to exploring the factors contributing to PSF in order to lead the development of future treatment options; this study attempted to fulfill this goal by introducing physiologic measures to aid assessing PSF. This study aimed to 1) distinguish EF from CF, 2) identify contributing factors of EF and CF in people with PSF, and 3) develop a model that is specific to PSF to guide clinicians and future research.

The findings of this study should aid clinicians implement individualized therapeutic treatment according to the presence and magnitude of each contributing factor. More specifically, if a physical therapist could detect the contributing factor(s) to a person's post-stroke fatigue, he or she can implement treatments based on the nature of such factor(s). The capability of detecting the types of fatigue also helps to pinpoint potential contributing factors. For example, if EF is observed, it is possible that diminished aerobic fitness is the most substantial factor to a person's

PSF. In this case, aerobic fitness training may be prescribed and incorporated in addition to the standard physical therapy treatments. On the other hand, if a person's PSF is determined to be largely contributed by medication side effects, perhaps simply by consulting with the primary physician to alter medication or to reduce dosage could help alleviate the fatigue issues. If depression is detected to be the most hindering factor to a person's PSF, counseling, social outings, and family support may be the key solutions to the person's fatigue issue. It is important to acknowledge the fact that PSF is multidimensional, and so should the treatments. In addition, the findings of this study also contribute to the validity of the multidimensional fatigue model in the literature by confirming two of the potential contributing factors.

1.9 Specific Aims and Statement of Hypotheses

The primary goal of this project was to investigate fatigue issues by characterizing the nature of different types of fatigue in people with chronic stroke. Two central aims guided this research:

1. Assess predictors of exertion fatigue in people with chronic stroke. (Chapter 3)

The first aim of this dissertation project was to identify the potential contributing factors of exertion fatigue (EF) in people post-stroke using multiple linear regression where the response variable is EF and the explanatory variables are aerobic fitness (measured by VO_{2peak}), motor control (measured by FMTM), and depressive symptoms (measured by GDS). It was hypothesized that VO_{2peak}, FMTM score, and GDS score will simultaneously predict the presence and severity of EF.

1a. Assess the reliability, responsiveness, and validity of the Visual Analog Fatigue Scale in people post-stroke (Chapter 2).

Due to the lack of adequate instrument to differentiate and to measure different types of fatigue, we developed the Visual Analog Exertion Fatigue Scale (VAFS) to overcome the inadequacy of measurement method. The VAFS is a clinically feasible tool specifically designed to assess the level of exertion or chronic fatigue in people post-stroke. The research data of this dissertation project relied on the validation of the VAFS to measure fatigue level in people post-stroke. Therefore, we assessed the reliability, responsiveness, and validity of the VAEFS and found that VAFS is a reliable and valid tool to access fatigue in people with chronic stroke.

2. Assess predictors of chronic fatigue in people with chronic stroke. (Chapter 4)

The second aim of this dissertation project was to identify the potential contributing factors of CF in people post-stroke using multiple linear regression where the response variables are two CF measures (i.e. $VAFS_{at\text{-}rest}$ and FSS) and the explanatory variables are aerobic fitness (measured by VO_{2peak}), motor control (measured by FMTM), and depressive symptoms (measured by GDS). It was hypothesized that

VO_{2peak}, FMTM score, and GDS score will simultaneously predict the presence and severity of CF.

In summary, the research presented in this dissertation contributes to the existing body of literature through 3 separate and distinct manuscripts. The first manuscript attempts to address the fatigue assessment validity issue in people post-stroke (Chapter 2, to be submitted to *Physical Therapy*); the second and third manuscripts attempt to differentiate fatigue with different nature and define its predictors in people post-stroke (Chapter 3 & 4, to be submitted to *Physical Therapy*).

Figure 1.1 Illustration of Piper's fatigue model. We developed this illustration based on Piper's original conceptual framework of fatigue.[32]

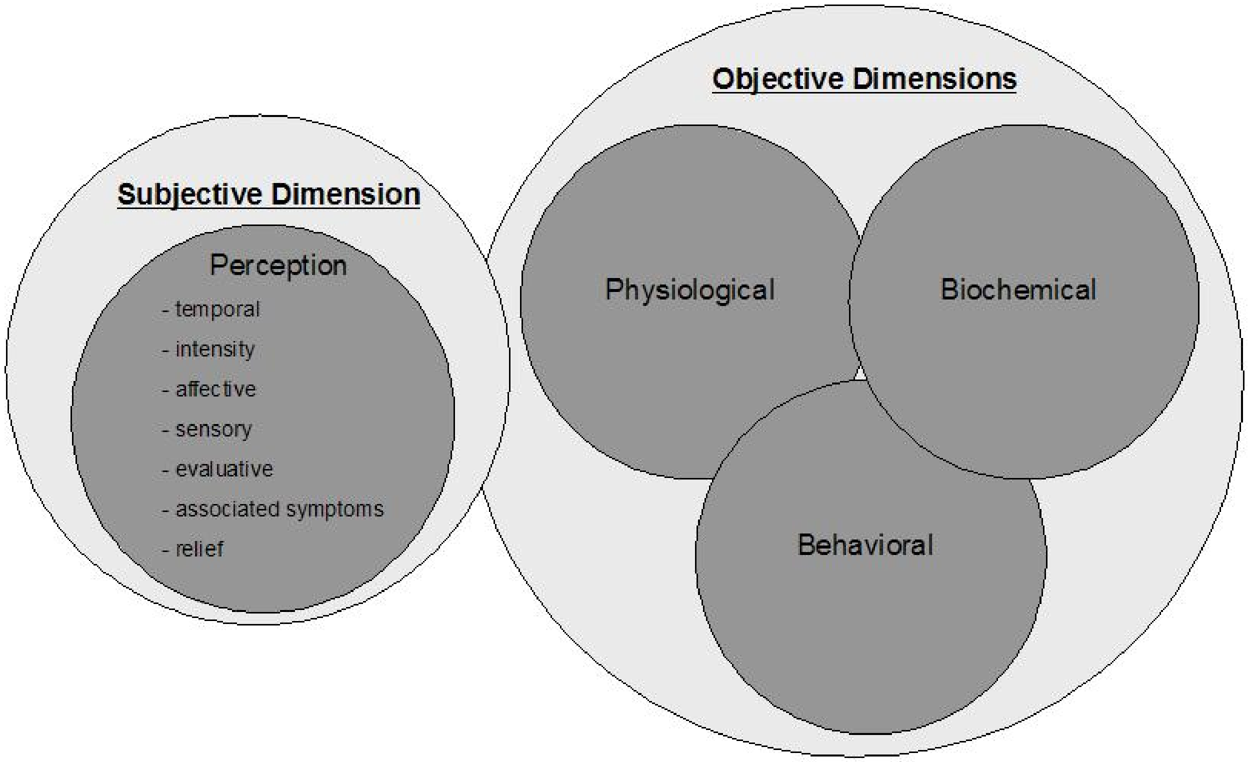


Figure 1.2 Illustration of Portenoy's fatigue model. We developed this illustration based on Portenoy's integrated fatigue conceptual framework.[52]

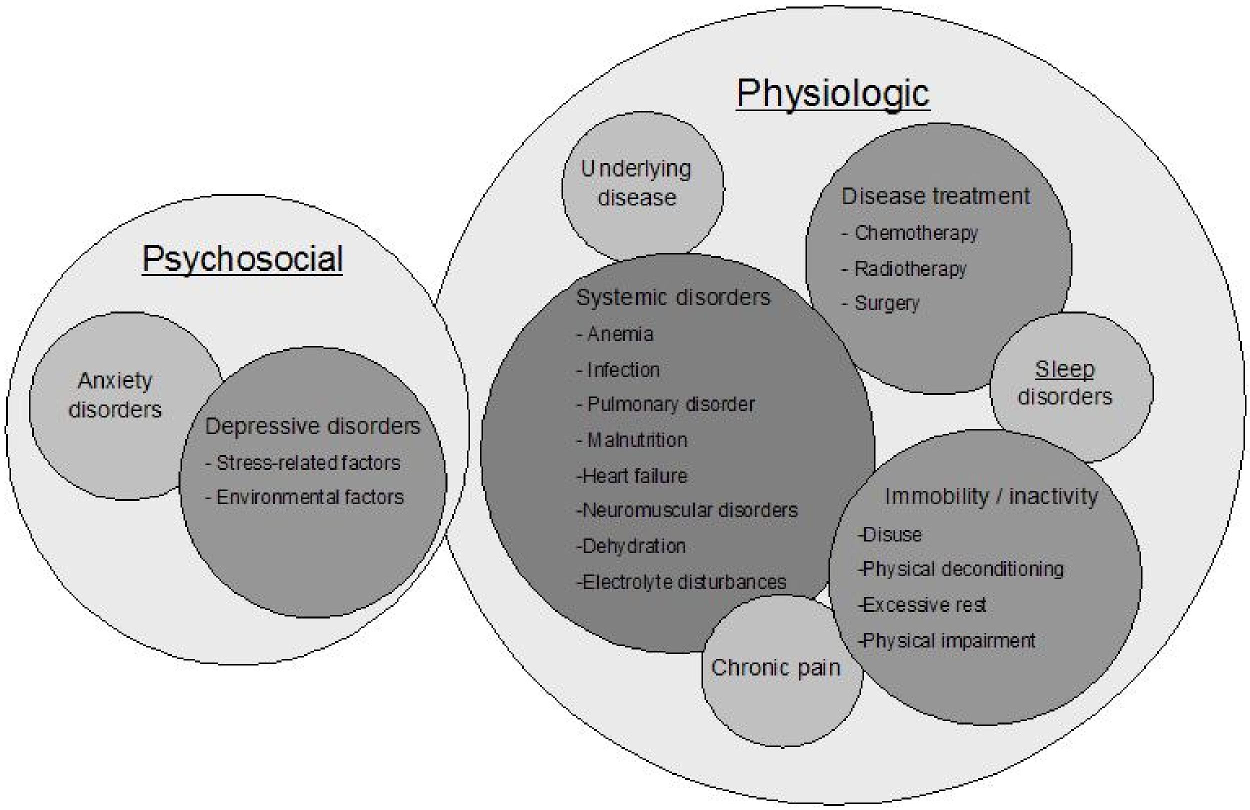


Figure 1.3 Illustration of Piper's dichotomy fatigue concept with duration, onset, and recovery rate as key distinctive indicators. We developed this model based on Piper's dichotomy fatigue concept.[53]

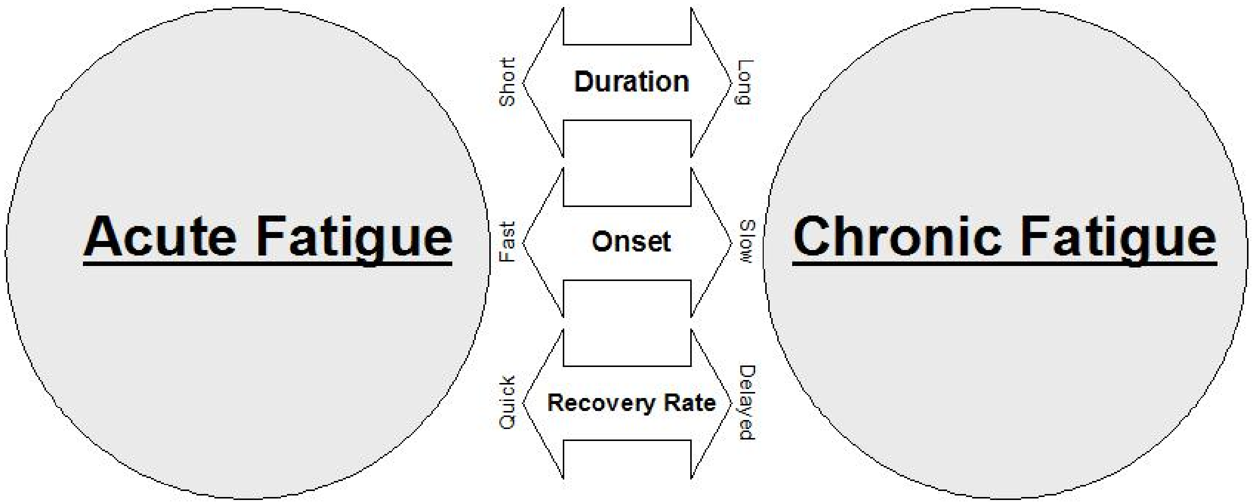
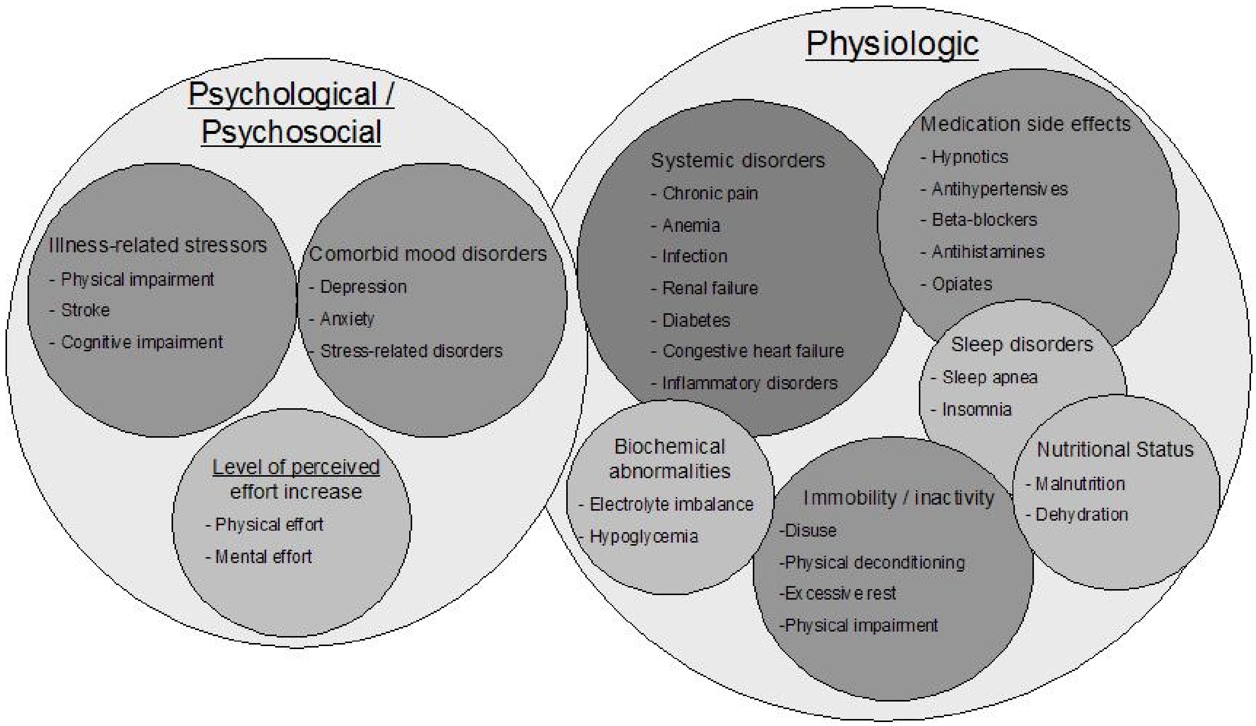


Figure 1.4 Contributing factors to Post-Stroke Fatigue. We developed this model based on the potential fatigue contributing factors specific to people-stroke proposed by de Groot et al.[20]



Chapter 2 Preface

Chapter 2 is the development of the Visual Analog Fatigue Scale (VAFS) for assessing fatigue in people post-stroke. This chapter attempted to address the need for a valid assessment tool specifically designed for people post-stroke to quantify fatigue. The work presented in this chapter examined the reliability, responsiveness, and validity of the VAFS. The results suggest that the VAFS is a valid and reliable tool to assess fatigue in people post-stroke. The VAFS was used as the main fatigue measurement in Chapter 3 and 4.

Chapter 2

Reliability, Responsiveness and Validity of the Visual Analog Fatigue Scale to Measure Exertion Fatigue in People with Chronic Stroke

To be submitted to *Physical Therapy*, February, 2009

2.1 Abstract

Background and purpose: Post-stroke fatigue (PSF) is prevalent among survivors of stroke; however, it is commonly neglected by health professionals. To date, defining and measuring fatigue has remained a challenge as fatigue is a multifactorial phenomena that involves both physiological and psycosocial properties. The lack of understanding and valid measurement may facilitate concealment this overlooked public health issue. To address the inadequacy of assessment methods to measure fatigue in people post-stroke, we developed the Visual Analog Fatigue Scale (VAFS). **Methods:** Twenty-one people post-stroke (12 males, 9 female, age = 59.5 ± 10.3 years; time post-stroke = 4.1 ± 3.5 years) participated in the study. This experiment involved 2 separate visits that were conducted 14 days apart. The first visit involved a 15-minute sub-maximal fatigue-inducing exercise and fatigue assessments using the Visual Analog Fatigue Scale (VAFS) at 3 different time points (i.e. at rest, post-exercise, post-recovery). Subjects were allowed 15 minutes for recovery. In addition, heart rate (HR), blood pressure (BP), and the Rate of Perceived Exertion (RPE) were recorded during exercise. The second visit consisted of the same procedures as the first visit. **Results:** Good intra-rater reliability was found for the VAFS measures taken during the 2 separate sessions (at rest ICC = 0.851, CI = 95%, 0.673 ~ 0.936, $p < 0.001$; immediately after exercise ICC = 0.846, CI = 95%, 0.663 ~ 0.934, $p < 0.001$; post-exercise ICC = 0.888, CI = 95%, 0.749 ~ 0.953, $p < 0.001$). Exertion Fatigue (EF) was calculated ($VAFS_{post\text{-}exercise} - VAFS_{at\text{-}rest}$) and increase of HR and BP were determined (i.e. HRI and BPI, respectively). Using Pearson's

correlation coefficient, a significant positive relationship was found for EF and HRI ($r = 0.738$; $p = 0.00$); EF and SBPI ($r = 0.630$; $p = 0.02$); and EF and RPE ($r = 0.802$; $p = 0.00$). **Conclusion:** The results suggest that the VAFS is a valid and reliable tool to assess fatigue in people post-stroke.

2.2 Introduction

Post-stroke fatigue (PSF) is a prevalent symptom among survivors of stroke,[11, 14-17, 20, 71, 72] with an incidence rate as high as nearly 70%.[11, 64] However, it is a commonly neglected issue by clinicians as well as care-givers.[11, 14-17] More recently, researchers have begun to explore the negative ramifications of PSF on stroke rehabilitation.[16, 65, 66, 71, 112] For example, survivors of stroke with PSF may have a higher fatality rate three years after stroke due to a sedentary lifestyle.[15] PSF affects performance of daily activities, especially those requiring physical effort,[18] which may limit participation in a rehabilitation program. Nevertheless, defining and measuring fatigue has remained a challenge as it is a multifactorial phenomena that involves both physiological and psycosocial properties.[32, 37]

Fatigue has been defined as a feeling of early exhaustion, weariness, lack of energy and aversion to effort.[17] However, this definition does not distinguish the nature of different types of fatigue. It has been suggested that fatigue can be an everyday experience that most individuals report after exertion of physical power or use of mental effort.[35] Researchers have distinguished this type of fatigue as "exertion fatigue" (EF) that is attributed to extensive activities throughout daily living.[53, 55, 56] Exertion fatigue is acute in nature with a rapid onset and short duration, and can be recovered by rest. On the other hand, "chronic fatigue" (CF) is differentiated from EF and is defined as a state of weariness unrelated to previous exertion levels that is associated with prolonged stress or pathologies.[53, 56] The cause of chronic fatigue is uncertain; but several factors may contribute to chronic fatigue such as depressive symptoms,[14, 58-60] cancer related treatments,[57] and medication side-effects.[35]

To assess fatigue, many unidimensional[27, 34, 57] and multidimensional[29, 35, 54, 61] questionnaires and scales have been developed. Although it is controversial to determine which fatigue scales are the most accurate and appropriate to assess PSF, it has been suggested that the appropriateness of a fatigue scale should be determined by aspects of fatigue that are being measured.[62] It has been proposed that the Dutch Exertion Fatigue Scale (DEFS)[55] can be used to assess exertion fatigue in patients with heart disease, postpartum women, and patients living in a home for the elderly. However, it has not been validated in people with chronic stroke. In a recent study in Sweden,[71] fatigue was assessed by asking survivors of stroke whether they had experienced fatigue and/or pain after the stroke with a yes/no response. Subjects were also asked whether they felt their fatigue was stroke related. This study was able to determine the prevalence of PSF; however, it was not able to detect the severity or to identify different types of PSF. In Taiwan, researchers used the Situational Fatigue Scale (SFS)[54] that specifies the nature and the duration of daily activities to assess fatigue in healthy adults. The results revealed internal consistency and test-retest reliability and suggested that the SFS could be a useful tool to measure the broad concept of fatigue. However, several items in the SFS were too specific to the types of activity involved and may not applicable to clinical population with physical limitations (e.g. playing a ball game for 30 min, jogging for 20 min, or driving for 1hour).

In people post-stroke, the most commonly used scales are the Fatigue Severity Scale (FSS)[11, 16, 64-66] and the Visual Analog Scale (VAS)[16, 65, 70] to assess PSF. Choi-Kwan and colleagues[16] studied PSF in 220 survivors of stroke using VAS and FSS. They found that 57% of people post-stroke had fatigue problems and concluded that PSF is a common complaint among people post-stroke. In 2006, Michael and colleagues[65] investigated how mobility, aerobic fitness, and social support are related to fatigue in 53 people post-stroke. The severity of fatigue was examined using both VAS and FSS. They found that subjects with higher fatigue scores had lower social support and poorer falls efficacy scores than those with less fatigue. In addition, Underwood and colleagues[70] examined changes in pain and fatigue in 32 people receiving a 2-week constraint-induced movement therapy (CIMT). Fatigue was evaluated using VAS twice daily during therapy. They concluded that CIMT therapy may be administered without exacerbation of pain or fatigue. Although VAS was used to assess PSF in these studies, the reliability and the validity of VAS were not reported; and the types of PSF were not identified or differentiated.

Regardless of all previous effort, there is still a need to validate fatigue assessments for people with PSF.[113] To the author's best knowledge, no study has yet to differentiate different types of PSF using a simple, reliable and quantifiable measure in people with chronic stroke. We developed the Visual Analog Fatigue Scale (VAFS) as a vertical scale to assess PSF. In this study, a vertical version of VAS was utilized in order to eliminate subject difficulties and poor data validity due to visual field defect, neglect or other visual-perceptual deficits experienced among people following stroke. The VAFS is modified from a previously validated vertical version of VAS that was designed to assess sleep-related breathing disorders in people post-stroke[109]. The purpose of this study was to evaluate the reliability, responsiveness, and validity of the VAFS to assess PSF in people with chronic stroke at rest and following exercise. We hypothesized that VAFS will show 1) good intra-rater reliability at rest, immediately post-exercise, and 15-minutes post-exercise; 2) a significant effect size of VAFS score change before and immediately after exercise; and 3) a direct positive relationship with physiologic measures (i.e. heart rate and systolic blood pressure) and the Rate of Perceived Exertion Scale (RPE).[68, 69]

2.3 Methods

Experimental Design

This study used a sample of convenience to determine intra-rater reliability and validity of the VAFS in people with chronic stroke.

Participants

Twenty-one subjects participated in the study. Individuals were recruited from local stroke support groups and the ASTRA (Advancing Stroke Treatment through Research Alliances) participant database. To be included in this study, all participants must: 1) have a diagnosis of stroke $\geq$ 6 months and $\leq$ 5 years ago, 2) have the ability to perform the exercise movement on a total body recumbent stepper, 3) receive medical clearance from their primary care physician to confirm that subject is medically stable and able to participate in exercise, and 4) score < 2 on a dementia screening tool, the AD8.[114, 115] Subjects were excluded from the study if they presented with any of the following:

- Hospitalization for myocardial infarction, heart surgery, or congestive heart failure during the preceding 3 months.
- Recent symptoms of chest discomfort.
- Resting blood pressure of 160/100 or greater.
- Currently using a pacemaker.
- Currently smoking or significant pulmonary pathology.
- Alcoholism or alcohol dependency.
- Recreational drug use.
- Medication change within the duration of the study (e.g. antidepressants, cardiac medications).

The Human Subjects Committee at the University of Kansas Medical Center approved the study. Institutionally approved informed consent was obtained in writing prior to participation in the study.

Procedure

The first visit involved fatigue-inducing exercise and VAFS at 3 different time points. Prior to the exercise, subjects were presented with the VAFS for the first time to measure fatigue at rest ($VAFS_{at\text{-}rest1}$). Next, subjects were asked to perform a 15-

minute standardized fatigue-inducing exercise. During exercise, heart rate, blood pressure, and the Rate of Perceived Exertion (RPE)[68, 69] were recorded every 5 minutes. Immediately followed the exercise, the VAFS was again administered ($VAFS_{post\text{-}exercise1}$). Subjects were allowed 15 minutes for recovery; then they were presented the VAFS for the third time ($VAFS_{post\text{-}recovery1}$). A second visit was scheduled 14 days after the first visit. Best effort was given to keep exercise testing and data collection at the same or similar time of the day as the first visit. The actual sequence of the second visit was identical to the first visit. Fatigue scores were assessed at rest, immediately after exercise, 15 minutes after exercise ($VAFS_{at\text{-}rest2}$, $VAFS_{post\text{-}exercise2}$, $VAFS_{post\text{-}recovery2}$, respectively).

Visual Analog Fatigue Scale (VAFS). Traditionally, a visual analog scale VAS[82], [116] consists of a 10 cm horizontal line with written descriptions at each end; subjects are asked to mark on the line the point that they feel represents their perception of their current state (Figure 2.1). Verbal instruction was given. Subjects were asked by the test administrator "Using the vertical line on the Visual Analog Fatigue Scale, please draw a line to indicate how tired you are at this moment." The possible score ranges from 0 to 100, measured in millimeters on a 10cm vertical line using a pen. The score was obtained by measuring the line from "No Fatigue" to the point indicated by the subject that represents their fatigue level; the higher the VAFS score, the higher the fatigue. To avoid bias associated with the position of the text description on the VAFS (e.g. top is higher), two different versions were administered in random order. Version 1 indicated “Very Severe Fatigue” on top of the 10cm line and “No Fatigue” below the same vertical line; while version 2 had an opposite arrangement to represent the perceptions (Figure 2.1). The same version of VAFS was used at 3 different time points on the same day; subjects who received Version 1 on the first visit were administered Version 2 on the second visit.

Physiologic Responses. Heart rate and blood pressure were measured at rest and every 5 minutes during exercise. Heart rate increase (HRI) and systolic blood pressure increase (SBPI) were calculated and used for analysis.

Rate of Perceived Exertion (RPE). The RPE[68, 69] was used to determine the highest level of effort exerted perceived by subjects. It was recorded every 5 minutes during the fatigue-inducing exercise.

Fatigue-Inducing Exercise. To induce EF, subjects were asked to perform a 15-minute standardized exercise protocol on a total body recumbent stepper (NuStep, Inc; 5111 Venture Drive Suite 1, Ann Arbor, MI 48108). To standardize the workload, all subjects were asked to step at 75 step per minute (SPM) with an external power of 75-80 Watts (W) for 15 minutes. The device and workload of our fatigue-inducing protocol was based on the Modified Total Body Recumbent Stepper Exercise Test (mTBRS-XT)[117] our lab has developed to induce fatigue at a sub-maximal level, which allows subjects to become safely fatigued at 40-70% of VO_{2Max}.[118]

Data Analysis

SPSS 15.0 (SPSS, Inc; 233 S. Wacker Drive 11th Floor Chicago, IL 60606) statistical software was used to perform all statistical analysis; alpha level of 0.05 was used to determine statistical significance. Descriptive statistics were calculated. EF was calculated by subtracting $VAFS_{at\text{-}rest}$ score from $VAFS_{post\text{-}exercise}$ score ($VAFS_{post\text{-}exercise}$ – $VAFS_{at\text{-}rest}$). Recovery Rate (RR) was calculated as the percentage using this formula: ($VAFS_{post\text{-}exercise}$ – $VAFS_{post\text{-}recovery}$) / ($VAFS_{post\text{-}exercise}$ – $VAFS_{at\text{-}rest}$) x 100.

Intra-rater Reliability. To determine intra-rater reliability, the intraclass correlation coefficient ($ICC_{3,1}$) was calculated for all appropriate pairs of repeated measure taken during Visits 1 and 2 (i.e. $VAFS_{at\text{-}rest1}$ vs $VAFS_{at\text{-}rest2}$, $VAFS_{post\text{-}exercise1}$ vs $VAFS_{post\text{-}exercise2}$, $VAFS_{post\text{-}recovery1}$ vs $VAFS_{post\text{-}recovery2}$, EF_1 vs EF_2, and RR_1 vs RR_2). Bland-Altman plot was used to examine the shift in the measurement and the variability in the VAFS change score.

Responsiveness. To examine the ability of the VAFS to detect change over time, the Effect size (ES) was calculated as an index of responsiveness using the formula ES = mean ($VAFS_{post\text{-}exercise}$ – $VAFS_{at\text{-}rest}$) / standard deviation $VAFS_{post\text{-}}$

exercise.[119] In addition, paired t-test was used to determine difference between scores at-rest and post-exercise, and between post-exercise and post-recovery.

Validity. The peak RPE values were used for analysis; heart rate increase (HRI) and systolic blood pressure increase (SBPI) were calculated by subtracting respective values at rest from the peak values during the exercise. Pearson's correlation coefficient was used to determine the relationship between EF and HRI, EF and SBPI, and EF and RPE.

2.4 Results

Characteristics of the 21 subjects are shown in Table 2.1. One subject was only able to complete 5 minutes of the 15-mminute fatigue-inducing protocol and requested early termination due to fatigue and shortness of breath in both visits. Although subject reported high level of exertion fatigue, no chest pain and any adverse event was observed.

Reliability of the VAFS

Good[120] intra-rater reliability was found for the VAFS measures taken during the 2 separate sessions. ICC values for the VAFS at rest was 0.851 (CI = 95%, 0.673 ~ 0.936, $p < 0.001$), immediately after exercise was 0.846 (CI = 95%, 0.663 ~ 0.934, $p < 0.001$), and 15 minutes after exercise was 0.888 (CI = 95%, 0.749 ~ 0.953, $p < 0.001$) as shown in Table 2.2. The VAFS measures of both visits are illustrated in

Figure 2.2; the Bland-Altman plot in Figure 2.3 illustrates the presence of a shift in the VAFS measure at rest, with relatively low variability. In addition, the Intra-rater reliability for the EF and the RR was also good[120] with the ICC values of 0.829 (CI = 95%, 0.631 ~ 0.927, $p < 0.001$) and 0.893 (CI = 95%, 0.760 ~ 0.955, $p < 0.001$), respectively.

Responsiveness

The ES values for at-rest to post-exercise and for post-exercise to post-recovery were 14.512 and 0.685, respectively. A large ES was found for the change in VAFS scores between at rest and immediately post exercise; and a moderate ES was found for the change between immediately post exercise and post recovery.[119] Using the paired t-test, significant difference was found between VAFS scores at-rest and post-exercise ($p < 0.001$), and between post-exercise and post-recovery ($p < 0.001$).

Validity Testing

HR Increase was 41.1 (± 14.9) beats per minute; SBP Increase was 37.1 (± 14.0) mmHg; and the RPE was 15.8 (± 2.9). A significant positive relationship was found using Pearson's correlation coefficient for EF and HRI ($r = 0.738$; $p = 0.00$); EF and SBPI ($r = 0.630$; $p = 0.02$); and EF and RPE ($r = 0.802$; $p = 0.00$). The relationship between the EF, HR, and SBP are illustrated in Figure 2.4 and 2.5, respectively.

2.5 Discussion

Our data demonstrated good intra-rater reliability of the VAFS at rest, immediately after exercise, and 15 minutes post-exercise. This finding supports our first hypothesis that the VAFS is a reliable instrument to assess PSF in people post-stroke. The VAFS also demonstrated good intra-rater reliability to measure exertion fatigue (EF) and recovery rate (RR). The VAS is commonly used to measure pain in clinical studies. For example, a study that examined the validity and reliability of the VAS in measuring acute abdominal pain found high reliability with ICC values of 0.990.[121] This finding is consistent with our study to suggest good intra-rater reliability for the measures taken at separate times. However, several fatigue studies that utilized the original VAS to assess PSF did not establish reliability or validity and used a simple measure to describe a complicated, poorly-defined phenomenon.[16, 65, 70]

Strohschein and colleagues evaluated the validity and reliability of the Piper Fatigue Scale in 64 post-polio patients.[122] Subjects were asked to complete the Piper Fatigue Scale and the Chalder Fatigue Questionnaire. Convergent validity was shown with a strong positive correlation between Piper Fatigue Scale scores and Chalder Fatigue Questionnaire scores ($r = 0.80$; $n= 46$). Reliability was also demonstrated with the Piper Fatigue Scale's strong Intra-rater reliability with ICC value of 0.98 ($n = 20$). The authors concluded that the Piper Fatigue Scale is a valid and reliable tool for measuring fatigue in post-polio patients.

In 2003, Michelson and colleagues examined the Fatigue Assessment Scale (FAS), a 10-item fatigue measure, in 351 adults and found a high internal consistency and reliability (ICC = 0.77).[27] The authors conluded that the FAS is a potentially valuable assessment instrument with promising internal consistency reliability and validity.

Although previous fatigue scales reported good reliability and ICC values,[27, 122] these scales were not designed to measure EF and did not examine the responsiveness to change of fatigue level. In order to accurately measure EF, the VAFS must be administered at the appropriate time; and to calculate EF, values need to be determined by subtracting the VAFS score at baseline from the score assessed immediately after exercise.

The VAFS demonstrated large responsiveness to changes between at rest and immediately after exercise, and moderate responsiveness between immediately after exercise and 15 minutes post-exercise, as determined by the ES. An ES value of 0.4 is considered small, 0.5 is considered moderate, and 0.8 and greater is viewed as large.[119] Our analysis was designed to examine the ability of the VAFS to detect immediate change of fatigue level due to exercise over a short period of time; changes of long-term fatigue level due to exercise training effect over a prolonged time period was not intended as part of our analyses.

Our data showed a significant positive relationship between the fatigue induced by exercise (measured by EF) and physiologic responses (i.e. hear rate and blood pressure, measured by HRI and SBPI, respectively). We also found a significant positive relationship between EF and subjectively perceived level of exertion (measured by RPE). The RPE and VAFS measure different constructs, as the RPE reflects the perceived level of exertion during exercise, not the level of exertion fatigue after exercise. In addition, by using VAFS, subjects are required to base their answers on intuitive response at the moment, which may help avoid recollections of previous references that are verbal or numerical. These findings indicate that VAFS is a valid instrument to measure fatigue following exercise in people with chronic stroke.

Consistent with the findings of Choi-Kwan and colleagues,[16] we found a high prevalence of fatigue in people post-stroke. Using the VAFS, we found evidence of baseline fatigue (Appendix I) in most subjects (20 out of 21) at rest prior to fatigue-inducing exercise. This discovery indicates that this type of baseline fatigue can exist independently of physical stress, which supports previous findings[15] to suggest a distinct construct in PSF that is persistent and chronic in nature. In 2002, Glader and colleagues conducted a follow-up study to investigate PSF in people 2 year post-stroke and concluded that PSF is frequent and can be persistent and chronic even late after stroke.[15]

One of the limitations in this study is the small sample size. Compared to other studies of scale development,[27, 57, 122] this study reported data based on a relatively small sample size. Although statistical significance was achieved, we were not able to do subgroup analyses to determine whether reliability and validity of VAFS would be different between gender, different types of stroke, and different times post stroke. We were unable to establish normative values of the VAFS in healthy populations due to the limited sample size. We acknowledge the absence of these comparison values as a limitation. Future studies may consider assessing fatigue using the VAFS in both young and older healthy adults.

Although baseline fatigued was detected, this study was not designed to distinguish other types of fatigue such as chronic fatigue or circadian fatigue (Appendix I). Future studies may consider measuring fatigue at different times of the day in order to detect such matters. Our data suggests two distinct constructs of PSF that are unique in nature; we also recommend that other types of fatigue measures could be used in future studies to detect other types of fatigue besides EF (e.g. chronic fatigue). Finally, future studies need to identify predictors of PSF in order to address fatigue issues with an intervention in people post-stroke.

2.6 Conclusion

In conclusion, the reliability, responsiveness, and validity of the Visual Analog Fatigue Scale (VAFS) appear to be promising when used to assess exertion fatigue in people with chronic stroke.

Figure 2.1 Illustration of (A) traditional visual analog scale used to measure pain, (B) VAFS Version 1, and (C) VAFS Version 2.
VAFS – Visual Analog Fatigue Scale

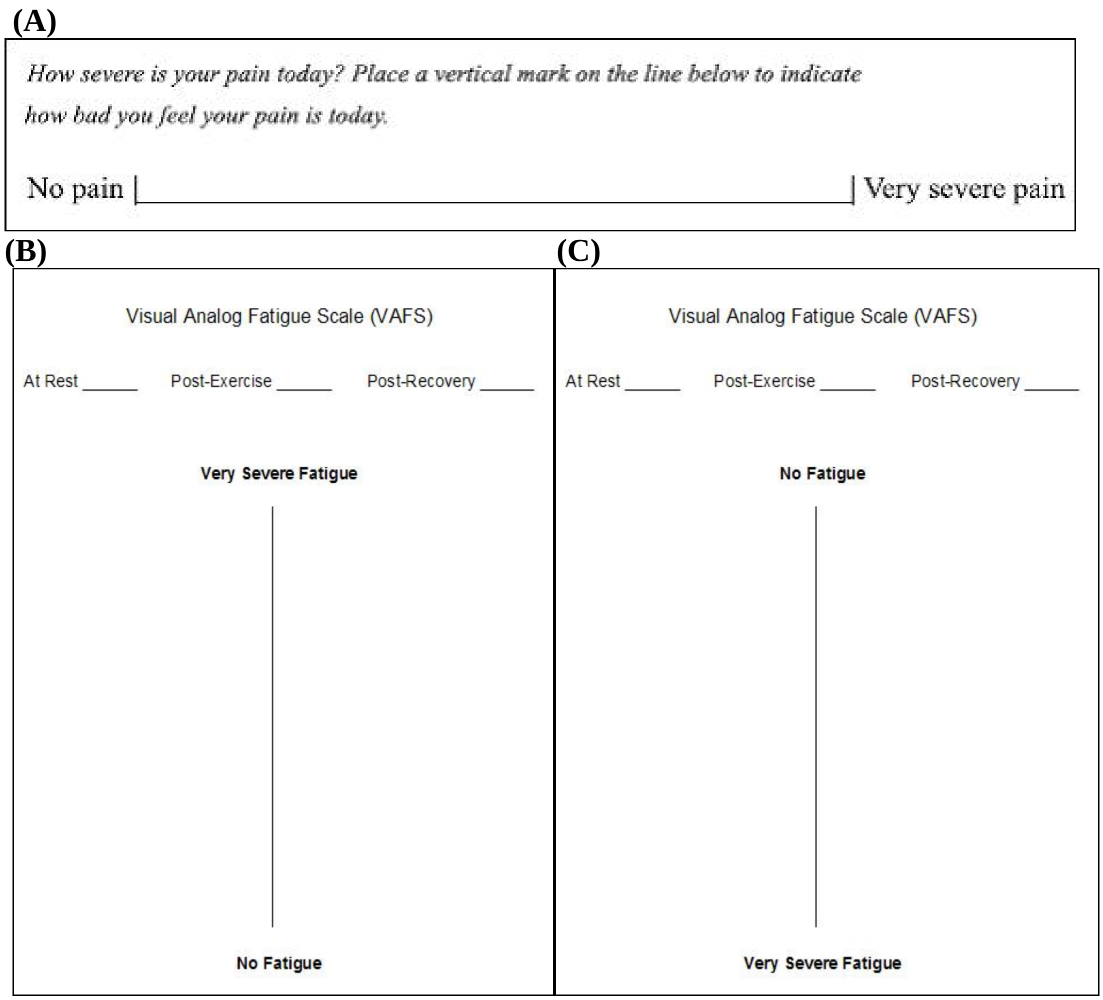


Figure 2.2 VAFS measures at-rest, post-exercise, and post-recovery from Visit 1 & 2.
VAFS – Visual Analog Fatigue Scale

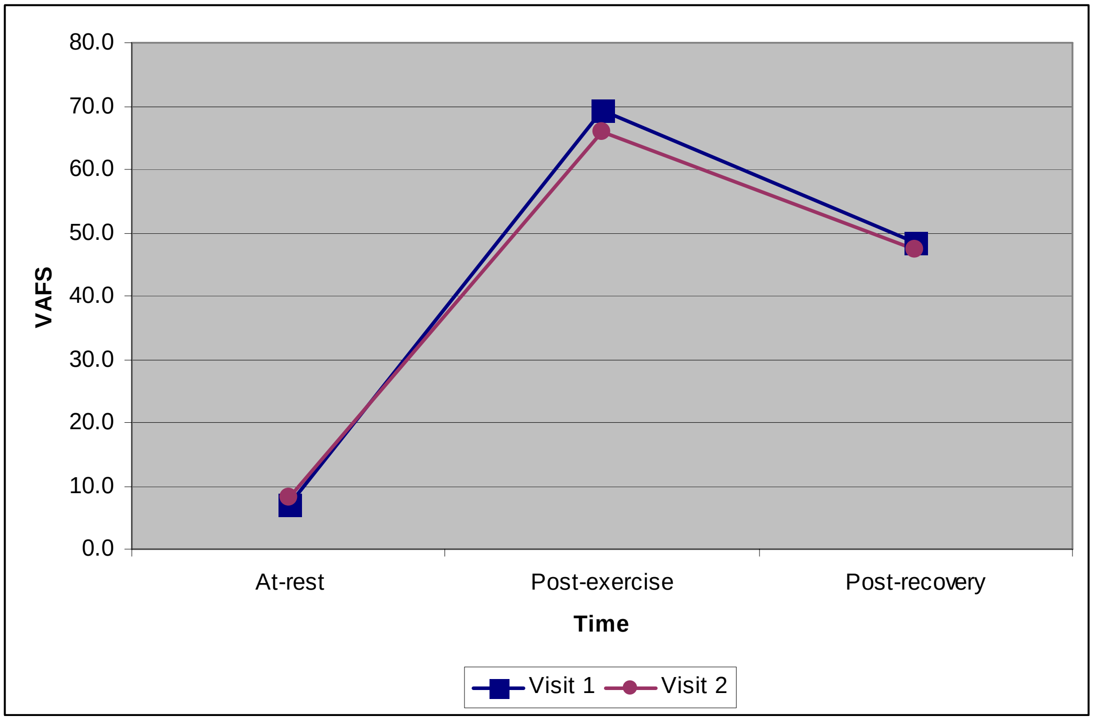


Figure 2.3 Bland-Altman plot of the VAFS scores at-rest from Visit 1 & 2 indicates no shift and low variability.
VAFS – Visual Analog Fatigue Scale

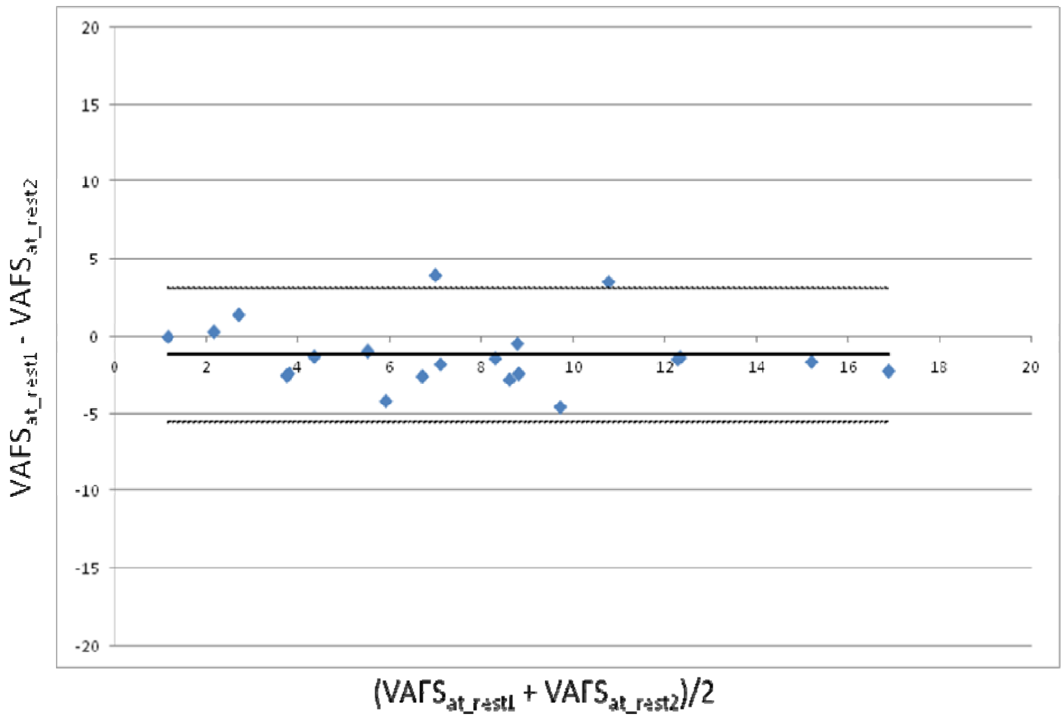


Figure 2.4 Scatterplot illustrating the relationship between EF and HR Increase.
EF – Exertion Fatigue
HR – Heart rate
BPM – beats per minute

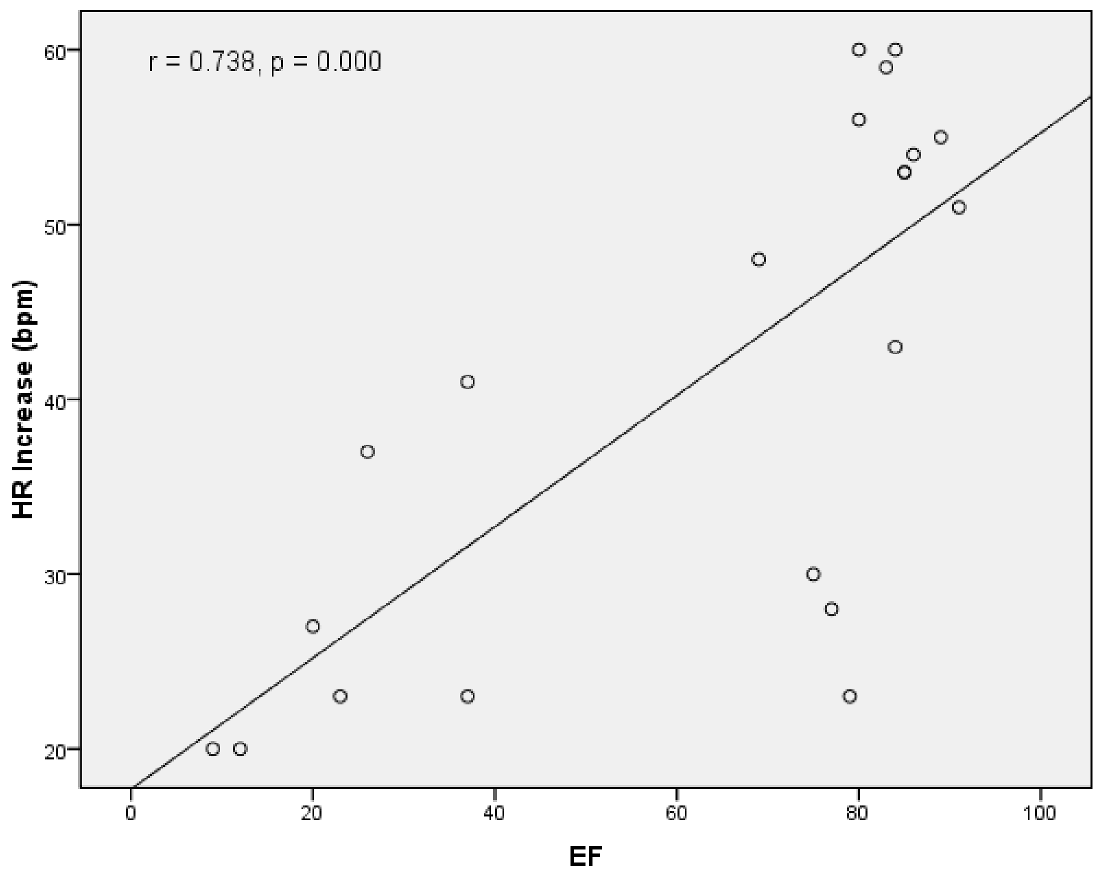


Figure 2.5 Scatterplot illustrating the relationship between EF and SBP Increase.
EF – Exertion Fatigue
SBP – Systolic Blood Pressure
mmHg – Millimeter of mercury

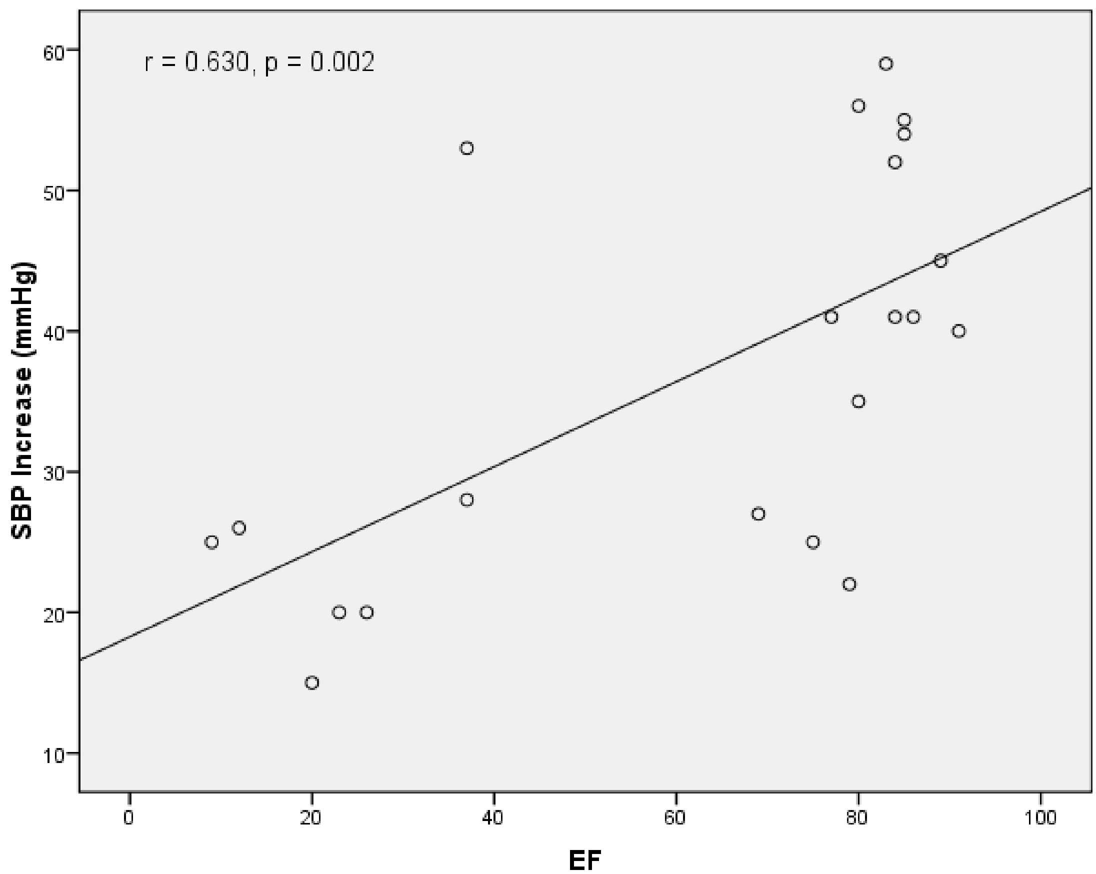


Table 2.1 Participant characteristics (n = 21). Values are means $\pm$ SD.

Characteristics	***Values***
Men / women	12 / 9
Stroke lesion side: right / left / brain stem	15 / 4 / 2
Stroke subtype: ischemic / hemorrhagic	18 / 3
Age (years)	59.5 ± 10.3
Time post-stroke (years)	4.1 ± 3.5

Table 2.2 The Intraclass Correlation Coefficient of measures on 2 separate visits (n = 21).

	Visit 1	***Visit 2***	***ICC***
$VAFS_{at\text{-}rest}$	7.2 ± 4.3	8.3 ± 4.5	0.851
$VAFS_{post\text{-}exercise}$	69.4 ± 30.5	65.8 ± 31.9	0.846
$VAFS_{post\text{-}recovery}$	48.5 ± 25.4	47.5 ± 26.9	0.888
EF	62.4 ± 29.3	57.5 ± 30.9	0.829
RR (%)	37.0 ± 17.3	37.7 ± 15.9	0.893

VAFS – Visual Analog Fatigue Scale
EF – Exertion Fatigue (EF = $VAFS_{post\text{-}exercise}$ – $VAFS_{at\text{-}rest}$)
RR – Recovery Rate (RR = $VAFS_{post\text{-}exercise}$ – $VAFS_{post\text{-}recovery}$) / ($VAFS_{post\text{-}exercise}$ – $VAFS_{at\text{-}rest}$) x 100
ICC – Intraclass correlation coefficient, model (3,1)
P – Probability Value

Chapter 3 Preface

Chapter 2 examined the reliability and validity of the Visual Analog Fatigue Scale (VAFS). We found that the VAFS is a valid and reliable tool to assess fatigue in people post-stroke.

In Chapter 3, we examined the Exertion Fatigue (EF) regression model using EF as the response variable (measured by the VAFS), and aerobic fitness, motor control and depression as explanatory variables (measured by VO2peak, Fugl-Meyer total motor, and Geriatric Depression Scale, respectively). We found that aerobic fitness was a good predictor for EF.

Chapter 3

Predictors of Exertion Fatigue in People Post-Stroke

To be submitted to *Physical Therapy*, February, 2009

3.1 Abstract

Background and purpose: Post-Stroke Fatigue (PSF) is a commonly neglected issue despite the high incidence rate reported in people post-stroke. It can impact daily functions and quality of life and has been linked with a higher mortality rate after stroke because of its association with sedentary lifestyle. Previous studies have identified exertion fatigue (EF) but have not distinguished its contributing factors using quantifiable outcome measures as predictors that are specific to PSF.

Methods: Twenty-one people post-stroke (12 males, 9 female, age = 59.5 ± 10.3 years; time post-stroke = 4.1 ± 3.5 years) participated in the study. At rest, participants were asked to report their level of fatigue using the Visual Analog Fatigue Scale (VAFS). Next, they underwent a standardized fatigue-inducing exercise on a recumbent stepper. Immediately after the exercise, the VAFS was administered again to assess the level of fatigue at the moment. Exertion fatigue (EF) was calculated by subtracting the VAFS score at-rest from the VAFS score post-exercise. The explanatory variables included aerobic fitness, motor control, and depressive symptoms measured by VO_{2peak}, Fugl-Meyer total motor (FMTM) scores, and Geriatric Depression Scale (GDS), respectively. **Results:** Using stepwise multiple regression, we found that that VO_{2peak} was an independent predictor of EF ($p = .006$) and explained 30.5% of variance in EF (adjusted $R^2 = .305$). **Conclusion:** We found that aerobic fitness is a strong independent predictor of EF in people post-stroke with PSF. In addition, the VAFS also detected fatigue prior to exercise that was independent of activities involved. It is important to acknowledge that EF a

unique construct of PSF that differs from other types of fatigue that are persistent or chronic in nature.

3.2 Introduction

Following a stroke, the incidence of post-stroke fatigue (PSF) has been reported to be as high as 76% 8 months after stroke,[123] and can persist in 75% of people even 26 months after stroke.[124] PSF affects performance of daily activities[18] and is associated with other negative ramifications such as poor quality of life[66] and higher fatality rate.[15]

A recent review study highlighted the scarcity of interventions directed at PSF, and concluded that there is a need to identify people most likely to experience PSF, to validate existing fatigue assessments, and to evaluate the efficacy of fatigue treatment in survivors of stroke.[113] However, before any effective countermeasure of PSF can be developed and implemented, it is essential to first identify the nature of PSF and its potential contributing factors.

Fatigue is difficult to define and measure.[37] Although it has been described as a feeling of early exhaustion, weariness, lack of energy and aversion to effort,[17] this definition does not distinguish the nature of different types of fatigue. Some have suggested that fatigue can be an everyday experience that most individuals report after exertion of physical power or use of mental effort.[35] Researchers have distinguished this type of fatigue as "exertion fatigue" (EF) that is attributed to extensive activities throughout daily living.[36, 55] The difference between fatigue and EF is that fatigue doe not necessarily have a relationship with the performing of activities; while EF is directly related to activities.[36] Exertion fatigue is acute in nature with a rapid onset and short duration, and can be recovered by rest.

In 1998, Tiesinga and colleagues followed up with their earlier investigation and developed the Dutch Fatigue Scale (DUFS) and Dutch Exertion Fatigue Scale (DEFS) to assess general fatigue and EF, respectively.[55] They tested the DEFS in 138 patients with chronic heart failure and suggested that the DEFS is a reliable, valid, and strong instrument to measure EF in clinical setting. The DEFS is a 9-item questionnaire with scores ranges from 0-36; each item is specific to an activity (e.g. walk for 30 minutes), however, some items lacked clarity of the intensity and duration of task described (e.g. shopping, take a shower standing). Although it has been suggested that the DEFS can be used to in different clinical populations such as patients with heart disease and women that are postpartum, it has not been validated in people with chronic stroke and does not involve real-time measures. Nonetheless, Tiesinga and colleagues pioneered a clinically feasible assessment and the conceptual groundwork for EF.

In 2003, de Groot and colleagues conducted a review study to address PSF and suggested several potential contributing factors specific to PSF.[20] Some of the physiologic factors include: immobility or inactivity such as physical impairment, deconditioning, and disuse; sleep disorders such as sleep apnea or insomnia; and medication side effects. Some of the psychologic factors include: depression, cognitive impairment, and altered levels of perceived effort. In this study, we examined three variables that are considered substantial contributors to PSF in previous investigations - aerobic fitness,[18, 20, 65] physical impairment,[14, 15, 20, 65] and depression.[11, 14-16, 20]

People post-stroke have diminished aerobic fitness.[10, 45, 77, 79] Previous studies have assessed the peak oxygen uptake (VO_{2peak}) of stroke survivors[77, 79] and reported low peak VO_2 levels (13 ml/kg/min ~ 16 ml/kg/min) among people post-stroke, which is only 50% of healthy older adults. A comparable reduction was reported in maximal walking velocity (1.02+/-0.28m/s) and endurance (294.1+/-120.2m) by conducting a six-minute-walk test.[78, 80] Aerobic exercise has been shown to increase aerobic fitness after stroke,[77, 78] and its effects on PSF is a subject worthy of study. More specifically, when studying EF, it is important to acknowledge the potential role of aerobic fitness. In this study, VO_{2peak} was assessed as a potential predictor of EF using a maximal effort graded exercise test on a total body recumbent stepper.[83]

People post-stroke often experience increased energy expenditure due to limitations such as decreased range of motion, muscle tone, mal-alignment, and other musculoskeletal problems, which lead to poor biomechanical efficiency (e.g. inadequate gait due to the inability to activate normal motor patterns).[78] Researchers have considered physical impairment as a contributing factor to PSF.[14, 16, 20, 65, 66] In 2006, Appelros et al examined pain and fatigue in 253 survivors of stroke at baseline and 1 year post-stroke and documented the general characteristics of the patients, stroke type, stroke severity and risk factors at baseline.[71] Fatigue was assessed by asking the subjects whether they had experienced fatigue which had started after the stroke. After 1 year survivors were examined with respect to residual impairment, disability, cognition and depression. Appelros found that fatigue was associated with physical disability and sleep disturbances. In this study, physical impairment was assessed using the FM total motor score (FMTM), which consisted of the combined scores from the upper extremity (UE) and the lower extremity (LE) portions of the FM test.[93]

In people post-stroke, depression is the only identified factor with a significant relation to PSF.[14, 17, 59] Nevertheless, fatigue can exist independently of depression.[11, 14-16] A mail-survey study in 2005 evaluated the characteristics of and the factors associated with PSF in 220 people post-stroke.[16] Choi-Kwan and colleagues reported that 57% of 220 people 15 months post-stroke had fatigue problems and 24% had post-stroke depression. In addition, 50% of the people without post-stroke depression also post-stroke fatigue. The authors concluded that fatigue is a common complaint among people post-stroke, and it can be independent of depression. Previous researchers have suggested that depression and depressive symptoms should be observed[66] while acknowledging other factors may also play a role in contributing PSF.[64] In this study, depression was assessed as a potential predictor of EF using the Geriatric Depression Scale (GDS).[74]

Scales have been developed to measure EF in patients with chronic heart failure, postpartum women, and patients living in a home for the elderly,[55] however, these measures have not been validated in people with chronic stroke. The most commonly used scales to assess PSF are the Fatigue Severity Scale (FSS)[11, 16, 64-66] and the Visual Analog Scale (VAS).[16, 65, 70] However, none of the previous studies described PSF by differentiating EF from other types of fatigue. We have developed the Visual Analog Fatigue Scale (VAFS) specifically for survivors of stroke to assess

EF and found good reliability, responsiveness, and validity (Chapter 2). Yet, the potential contributing factors of EF following stroke remain undetermined. To the author's best knowledge, no study has yet identified predictors of EF in people post-stroke using quantifiable outcome measures as predictors.

The purpose of this study was to identify the potential contributing factors of EF in people post-stroke using multiple linear regression where the response variable is EF and the explanatory variables are aerobic fitness (measured by VO_{2peak}), motor control (measured by FMTM), and depressive symptoms (measured by GDS).

3.3 Methods

Experimental Design

This study used a convenience sample and a cross-sectional design to determine the predictors of EF in people post-stroke using aerobic fitness, motor control, and depressive symptoms as potential contributing factors.

Participants

Twelve men and 9 women (59.5 ± 10.3 years, 4.1 ± 3.5 years post-stroke) participated in the study. Individuals were recruited from local stroke support groups and the ASTRA (Advancing Stroke Treatment through Research Alliances) participant database. To be included in this study, all participants must: 1) have a diagnosis of stroke ≥ 6 months and ≤ 5 years ago, 2) have the ability to perform the exercise movement on a total body recumbent stepper, 3) receive medical clearance from their primary care physician to confirm that subject is medically stable and able to participate in exercise, and 4) score < 2 on a dementia screening tool, the AD8.[114, 115] Subjects were excluded from the study if they presented with any of the following:

- Hospitalization for myocardial infarction, heart surgery, or congestive heart failure during the preceding 3 months.
- Recent symptoms of chest discomfort.
- Resting blood pressure of 160/100 or greater.
- Currently using a pacemaker.
- Currently smoking or significant pulmonary pathology.
- Alcoholism or alcohol dependency.
- Recreational drug use.
- Medication change within the duration of the study (e.g. antidepressants, cardiac medications).

The Human Subjects Committee at the University of Kansas Medical Center approved the study. Institutionally approved informed consent was obtained in writing prior to participation in the study.

Procedure

The experiment consisted of 2 visits. One visit involved assessment of exertion fatigue, a fatigue-inducing exercise, level of motor control and depressive symptoms. The other visit involved an assessment of the peak oxygen uptake using a calibrated total body recumbent stepper (NuStep, Inc; 5111 Venture Drive Suite 1, Ann Arbor, MI 48108). The 2 visits were scheduled 24-48 hours apart to allow recovery.

Assessment of Exertion Fatigue (EF). Visual Analog Fatigue Scale (VAFS) was used to assess the level of EF. The VAFS consists of possible score ranges from 0 to 100, measured in millimeters on a 10cm vertical line using a pen. Verbal instruction was given. Subjects were asked by the test administrator "Using the vertical line on the Visual Analog Fatigue Scale, please draw a line to indicate how tired you are at this moment." The score was obtained by measuring the line from "No Fatigue" to the point indicated by the subject that represents their fatigue level. The VAFS has been reported to have good reliability, responsiveness, and validity (Chapter 2). Subjects were presented the VAFS for the first time to measure fatigue at rest ($VAFS_{at\text{-}rest}$). Immediately followed a 15-minute standardized fatigue-inducing exercise, the VAFS was again administered ($VAFS_{post\text{-}exercise}$). Subjects were allowed 15 minutes for recovery; then they were presented the VAFS for the third time ($VAFS_{post\text{-}recovery}$). EF was calculated by subtracting $VAFS_{at\text{-}rest}$ score from $VAFS_{post\text{-}exercise}$ score ($VAFS_{post\text{-}exercise} – VAFS_{at\text{-}rest}$). In addition, Recovery Rate (RR) was calculated as the percentage using this formula: $(VAFS_{post\text{-}exercise} – VAFS_{post\text{-}recovery}) / (VAFS_{post\text{-}exercise} – VAFS_{at\text{-}rest}) \times 100$.

Standardized Fatigue-Inducing Exercise. To induce EF, subjects were asked to perform a 15-minute standardized exercise protocol on a total body recumbent stepper. To standardize the workload, all subjects were asked to step at 75 step per minute (SPM) with an external power of 75-80 Watts (W) for 15 minutes. In this study, the device and workload of the fatigue-inducing protocol was chosen to allow subjects to become safely fatigued at 40-70% of VO_{2Max}.[118]

Aerobic Fitness (VO_{2peak}). To assess aerobic fitness, a maximal effort graded exercise test was conducted using a calibrated metabolic cart and the mTBRS-XT protocol our lab has developed specifically for people post-stroke.[83] Subjects were asked to refrain from eating food for an hour and drinking caffeine for 2 hours prior to the test. According to the test protocol, subjects stepped at 80 steps-per-minute (SPM) with a gradually increasing level of resistance. A cool-down period of 4 minutes followed the end of the test. Each subject's ECG was monitored by a 12-lead ECG system during the exercise test. The exercise test was terminated using the following criteria: (1) the participant reached volitional fatigue and requested to end the test, (2) the participant's VO_{2peak} plateaued or decreased despite continuation of exercise, (3) the participant was unable to maintain the cadence, or (4) an adverse cardiovascular event or response to the exercise test was observed. The successful completion of the maximal effort graded exercise test (measured in VO_{2max}) was determined by reaching 1) the predicted maximal heart rate [(220-age), 2) the respiratory exchange ratio (RER > 1.1), and 3) plateau of VO_2 values despite continuation of exercise.[118] When the subjects were unable to achieve their maximal effort, the aerobic fitness level at the peak values were collected (measured in VO_{2peak}).

Fugl-Meyer (FM). The FM was used to determine the level of motor function in the hemiparetic limbs following stroke. The FM is a reliable and valid tool that was specifically designed as a clinical measure of sensorimotor impairment for stroke.[93] The total possible score is 124, which consists of sensation (FMSEN - 24), upper extremity (FMUE - 66), and lower extremity (FMLE - 34). Because the fatigue-inducing exercise in this study required motor performance of all four limbs, the combined total motor (FMTM) scores of the FMUE and FMLE were determined (FMTM = FMUE + FMLE)[95] and used for analyses.

Geriatric Depression Scale (GDS). The GDS is a questionnaire that includes 30 items that refer to affective, cognitive, and behavioral symptoms of depression to assess mood. It has been tested and used extensively with the older population with good validity and reliability.[74, 125] The possible score ranges from 0 to 30.

Data Analysis

SPSS 16.0 (SPSS, Inc; 233 S. Wacker Drive 11th Floor Chicago, IL 60606) statistical software was used to perform all statistical analysis. Descriptive statistics were calculated. Histograms for each variable were analyzed for normal distributions, and scatterplots were analyzed for outlying scores. A stepwise linear regression model with 3 predictors (VO_{2peak}, FMTM, and GDS scores) was calculated for exertion fatigue (EF). Correlations among variables were calculated with the Pearson correlation coefficient. The validity of each model was assessed through analysis of colinearity statistics (variance inflation factor) and Q-Q plots of unstandardized residuals. In addition, secondary analysis using Pearson's correlation coefficient was performed in order to explore the relationship between exertion fatigue (EF) and recovery rate (RR) after exercise, and between recovery rate (RR) and aerobic fitness (VO_{2Peak}). A 0.05 level of significance was used for all statistical tests.

Sample Size

Initially, it was proposed that 30 subjects with chronic stroke will be recruited. In order to maximize limited resources and to avoid over-recruitment of subjects, a planned interim analysis was conducted after the completion of data collection for 20 subjects. The goal of this analysis was to determine whether further recruitment is required in order to satisfy statistical significance. To reduce the chance of making a type I error, alpha level was set at 0.01 for the interim analysis.

Power calculations indicated that for the interim analysis, the twenty subjects had 70% power to detect explanatory variables in a multiple linear regression (with three explanatory variables) with an R-square of 0.27 or greater and have 80% power to detect explanatory variables with an R-square of 0.31 or greater. These calculations used were done at the alpha = 0.01 level, as we conducted an interim analysis after twenty subjects (nQuery Advisor 6.01, 1995-2005).

3.4 Results

Data was collected from 21 individuals with chronic stroke; 5 out of 21 subjects were able to reach their maximal effort (measured by VO_{2max}); while the other 16 subjects reached their peak effort (measured by VO_{2peak}) according to our termination criteria. The 5 subjects who reached maximal oxygen uptake had VO_2 values that ranged from 19.0 ml/kg/min to 33.1 ml/kg/min, which were higher than the group mean of 16.2 ml/kg/min. Out of 21 subjects, 1 subject was only able to complete 5 minutes of the 15-mminute fatigue-inducing protocol and requested early termination due to fatigue and shortness of breath in both visits. Although subject reported high level of exertion fatigue, no chest pain and any adverse event was observed. Subject characteristics are shown in Table 3.1. Descriptive statistics of all variables are shown in Table 3.2 and correlations among variables are shown in Table 3.3.

Using stepwise linear regression, we found the regression model for the EF with 3 variables (VO_{2peak}, FMTM, and GDS scores) was statistically significant, with VO_{2peak} as a significant individual factor that explained 30.5% of variance in EF. The result of this model is presented in Table 3.4. Using Pearson's correlation coefficient, significant correlations were found for RR and EF ($r = -0.649$; $p = 0.001$) and for RR and VO_{2Peak} ($r = 0.891$; $p < 0.000$), as shown in Figure 3.1 and 3.2, respectively.

3.5 Discussion

Our data suggests that VO_{2peak} is a significant individual predictor for Exertion Fatigue (EF); previous research was unable to reach this conclusion.[65] In 2006, Michael and colleagues investigated how aerobic fitness, mobility deficit, ambulatory activity, self-efficacy for falls, and social support are related to fatigue in 53 people post-stroke.[65] The severity of fatigue was examined using Fatigue Severity Scale (FSS)[34] and the Visual Analog Scale (VAS);[82] aerobic fitness was assessed at the peak level using a graded exercise protocol on a treadmill. In addition, timed 10-meter walks, the Berg Balance Scale, total daily step activity, the Medical Outcomes Study Social Support Survey, and the Falls Efficacy Scale were also administered. They found that 46% of people post-stroke had severe fatigue; fatigue showed an inverse relationship with falls efficacy and social support, but not with aerobic fitness or ambulatory activity.

Although Michael and colleagues used the VAS that is similar to our VAFS to assess fatigue, the timing the VAS assessment was not specific to exercise. Rather, it was a single-time-point assessment that measured "overall" fatigue severity of the testing day. This type of fatigue assessment can only represent general level of fatigue, but not the type of fatigue that is activity-related such as EF. In our study, the VAFS was administered before and after the fatigue-inducing protocol; and the EF was calculated by subtracting $VAFS_{at\text{-}rest}$ score from $VAFS_{post\text{-}exercise}$ score ($VAFS_{post\text{-}exercise} - VAFS_{at\text{-}rest}$). This method ensured that the fatigue being measured was valid and was solely attributed to the exercise given that challenged subject's aerobic fitness capacity.

In addition to the VAS, Michael and colleagues used the FSS to detect fatigue. Although the FSS has been previously established and used in several PSF studies,[11, 16, 64-66] it focuses on functional effect of fatigue over the previous week, which is chronic in nature. The FSS was not sensitive enough to detect the type of fatigue that is associated with real-time exertion (e.g. exercise, household activity, or social activities). Furthermore, Michael and colleagues used a treadmill to access peak oxygen uptake; the current study used the mTBRS-XT protocol[83] on a total body recumbent stepper. These discrepancies in testing methods may contribute to the contradicting findings between current and previous investigations.

Since approximately 76% of our subjects did not reach their maximal aerobic fitness capacity, the results should be interpreted with caution. Theoretically, if we were able to obtain VO_{2max} instead of VO_{2peak} from all subjects, we would likely report higher VO_2 values for those who didn't reach VO_{2max} as VO_{2peak} is an underestimation of the actual maximal values. It is our postulation that VO_{2max} would better predict EF than VO_{2peak} if it was used as one of the explanatory variables in our regression model, In that regard, the literature has shown that aerobic exercise can increase aerobic fitness in people post-stroke,[77, 78] and its effects on PSF merits further investigations.

Although previous researchers considered physical impairment as a contributing factor to PSF,[20, 71] we did not find that motor control ability in the hemiparetic limbs as an independent predictor of EF in this study. Although our fatigue-inducing protocol involved all 4 limbs, it is probable that our exercise did not challenge full motor control capability as it was performed on a total body recumbent stepper. Future studies may consider administering fatigue-inducing protocol that is task-specific and requires full range of motion and coordination of hemiparetic limbs such as mimicking cooking activities while standing in front of a simulated kitchen counter. This approach will further induce EF to a higher degree and may better capture the poor biomechanical efficiency and increased energy expenditure due to limited range of motion, muscle tone, and mal-alignment often experienced in people post-stroke. In addition, future studies may consider incorporating muscular endurance and strength measures (e.g. isokinetic device) in the regression model to describe EF instead of motor control measured by FM. Although some researchers have used FM as an indication of stroke severity or impairment;[95-97] muscular endurance and strength measures are direct measures of muscular properties and could perhaps describe EF more truthfully than FM.

We did not find depression as an independent predictor of EF in this study. This finding conflicts with previous research that suggested that depression is a significant factor relating to PSF in survivors of stroke.[64, 66] It has been suggested that fatigue and major depressive disorder are often comorbid with each other and are commonly associated with other psychiatric disorders such as increased risk for suicide; barriers to treatment such as treatment resistance; and medical conditions such as cardiovascular disease and diabetes mellitus.[104] Interestingly, some researchers also suggested that fatigue can also exist independently of depression.[11, 14-16] In this study, we used the VAFS to measure fatigue that is associated with exertion, which is different from the type of fatigue measured by the FSS in previous studies.[64, 66]

In addition, we found a positive relationship between aerobic fitness and recovery rate (RR); and a negative relationship between EF and RR. In other words, the better the aerobic fitness, the better the recovery after exercise; and the better the recovery, the lesser the fatigue experienced after exercise. This finding is comparable to Piper's dichotomy fatigue concept,[53] which differentiates acute and chronic fatigue based on duration of fatigue symptoms, onset of fatigue, and the recovery rate.[53] Unfortunately, we were unable to compare the RR data collected from our study with other populations due to the fact that no previous study has used real-time fatigue assessment to calculate recovery rate as we attempted. Nevertheless, a similar assessment of heart rate recovery (HRR) has been well documented in both healthy adults[126-128] and adults with coronary artery disease.[129-132]

HRR within the first few minutes of graded exercise has been associated with impaired clinical outcomes in people with coronary artery disease.[129] Abnormal HRR is defined as $\leq$ 12 beats/min for standard exercise testing, which may be a reflection of decreased vagal activity. Abnormal HRR is also a powerful predictor of overall mortality, independent of workload, the presence or absence of myocardial perfusion defects, and changes in heart rate during exercise.[129] In addition, HHR has been shown to have the same predictive power even after sub-maximal exercise.[126] Previous studies monitor HRR from 1 to 2 minutes post-exercise;[126-132] in our study, we allowed subjects 15 minutes to recovery from the standardized fatigue-inducing exercise. Although the recovery time of our protocol was substantially longer, HRR does not measure fatigue and cannot be made direct comparison with the RR data from our study.

PSF is a multifactorial phenomena that involves both physiological and psychosocial properties.[20] One particular model described by Piper and colleagues in 1987 addressed the multidimensional nature of fatigue and suggested that the contributing factors of fatigue can be perceptual, physiological, biomechanical, and behavioral.[32] According to Portenoy's integrated fatigue model[52] developed based on cancer patients, EF is closely associated with factors that are physiologic (e.g. inactivity and physical deconditioning) than those that are psychosocial (e.g. depression and anxiety). On the other hand, chronic pain, medical treatment side effects, sleep disorders, and depression may better describe chronic fatigue. These variations may explain the contradicting findings between current and previous investigations in regards of the relationship between depression and fatigue. It is our postulation that the impact of depression may be more influential in fatigue that is chronic is nature than in EF. In addition, we observed the existence of baseline fatigue in majority of people post-stroke and the evidence of a distinct construct of PSF that is persistent and unique from EF (Chapter 2). Future studies should consider depressive symptoms as one of the main psychological factors contributing to the type of PSF that is chronic in nature.

3.6 Conclusion

We found that aerobic fitness is a strong independent predictor of exertion fatigue (EF) in people post-stroke with fatigue complaints. PSF is prevalent and can have severe negative impacts in people post-stroke; it is crucial to acknowledge that EF is a unique construct of PSF that differs from other types of fatigue that are persistent or chronic in nature. In addition, our data suggests a direct relationship between aerobic fitness level and recovery rate and an inverse relationship between aerobic fitness level and EF. It is important for clinicians to understand the nature of fatigue and identify potential contributing factors, and to implement individualized therapeutic treatment.

Figure 3.1 Scatterplot illustrating the relationship between RR and EF.
RR – Recovery Rate
EF – Exertion Fatigue

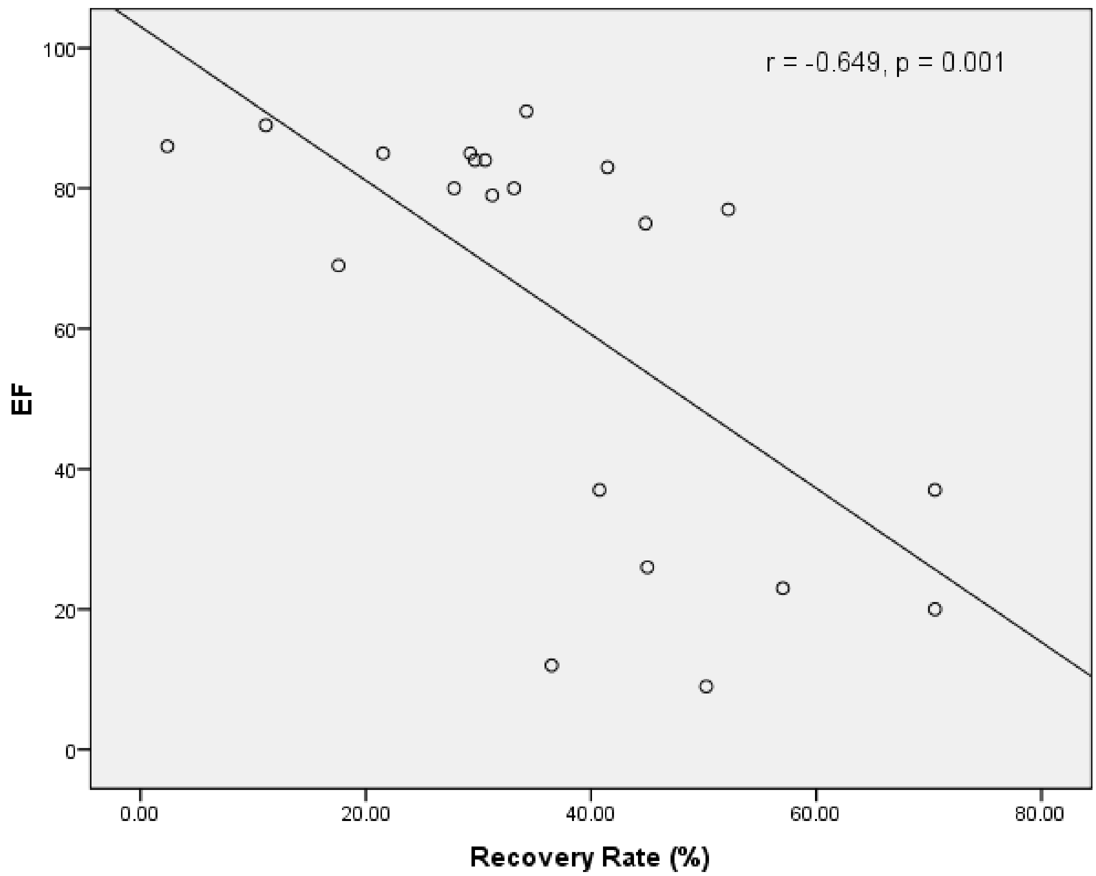


Figure 3.2 Scatterplot illustrating the relationship between RR and VO_{2peak}.
RR – Recovery Rate
VO_{2peak} – Peak Oxygen Uptake

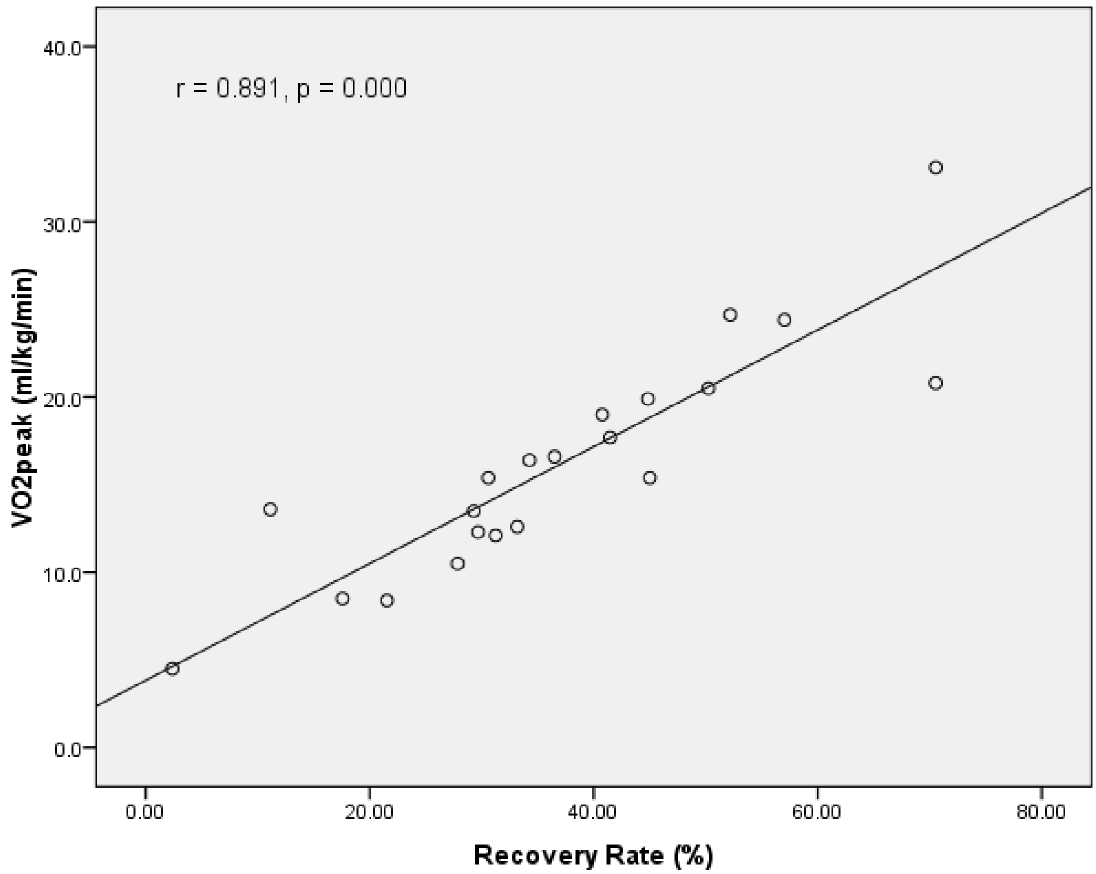


Table 3.1 Participant characteristics (n = 21). Values are means $\pm$ SD.

Characteristics	***Values***
Men / women	12 / 9
Stroke lesion side: right / left / brain stem	15 / 4 / 2
Stroke subtype: ischemic / hemorrhagic	18 / 3
Age (years)	59.5 ± 10.3
Time post-stroke (years)	4.1 ± 3.5

Table 3.2 Outcome measures (n = 21). Values are means ± SD.

Outcome Measures	**Values**
EF	62.4 ± 29.3
VO_{2peak} (ml/kg/min)	16.2 ± 6.5
FMTM	70.8 ± 28.8
GDS	10.2 ± 7.3
RR (%)	37.0 ± 17.3

EF – Exertion Fatigue
VO_{2peak} – Peak Oxygen Uptake
FMTM – Fugl-Meyer Total Motor
GDS – Geriatric Depression Scale
RR – Recovery Rate

Table 3.3 Pearson correlation among variables.

Variable	EF	VO_{2peak}	FMTM Score	GDS Score	RR
EF	1.000				
VO_{2peak} (ml/kg/min)	**-.582	1.000			
FMTM Score	-.270	.404	1.000		
GDS Score	.221	-.057	.159	1.000	
RR	**-.649	**.891	.495	-.123	1.000

**. Correlation is significant at the 0.01 level (2-tailed).

EF – Exertion Fatigue
VO_{2peak} – Peak Oxygen Uptake
FMTM – Fugl-Meyer Total Motor
GDS – Geriatric Depression Scale
RR – Recovery Rate

Table 3.4 Linear regression model for EF.

Linear Regression Model		
Adjusted R^2		0.305
F		9.76
P		0.006
Explanatory Variables	**B**	***P***
VO_{2peak}	-2.63	0.006
FMTM	-0.41	0.845
GDS	0.19	0.326

EF – Exertion Fatigue
VO_{2peak} – Peak Oxygen Uptake
FMTM – Fugl-Meyer Total Motor
GDS – Geriatric Depression Scale
P – Probability Values
B – Weights

Chapter 4 Preface

Chapter 2 examined the reliability and validity of the Visual Analog Fatigue Scale (VAFS) and found that the VAFS is a valid and reliable tool to assess fatigue in people post-stroke; while Chapter 3 examined the Exertion Fatigue (EF) regression model and found that aerobic fitness was a good predictor for EF. In addition, we also found that the VAFS was sensitive to the type fatigue that is persistent and chronic in nature (i.e. chronic fatigue or CF). This discovery led to the postulation that EF and CF may be 2 unique constructs each with its own contributing factors within the confine of post-stroke fatigue (PSF).

In Chapter 4, we examined Chronic Fatigue (CF) regression model using the VAFS and the Fatigue Severity Scale (FSS) scores as two response variables for CF, and aerobic fitness, physical impairment and depression as explanatory variables (measured by VO2peak, Fugl-Meyer total motor, and Geriatric Depression Scale, respectively). We found that depression is the independent predictor for CF regardless of assessment methods (VAFS or FSS).

Chapter 4

Predictors of Chronic Fatigue in People Post-Stroke

To be submitted to *Physical Therapy*, February, 2009

4.1 Abstract

Background and purpose: Post-Stroke Fatigue (PSF) manifestation can become a chronic issue that affects performance of daily activities long after stroke and leads to poor quality of life. However, not many health professionals recognize the unique nature of chronic fatigue (CF) as part of the PSF constructs and its impact on stroke rehabilitation effort. The purpose of this study was to identify the potential contributing factors of CF in people post-stroke. **Methods:** Twenty-one people post-stroke (12 males, 9 female, age = 59.5 ± 10.3 years; time post-stroke = 4.1 ± 3.5 years) participated in the study. The response variables included two CF assessments measured by the Visual Analog Fatigue Scale (VAFS) at rest and the Fatigue Severity Scale (FSS). The explanatory variables included aerobic fitness, motor control, and depressive symptoms measured by VO_{2peak}, Fugl-Meyer total motor (FMTM) scores, and Geriatric Depression Scale (GDS), respectively. **Results:** Using stepwise multiple regression, we found that that depression was an independent predictor of CF ($p < .001$) and explained 95.8% of variance in CF (adjusted $R^2 = .958$) when using the VAFS as the CF measure. When using the FSS scores as the CF measure, depression also explained 37.8% of variance in CF (adjusted $R^2 = .378$) as an independent predictor of CF ($p = .002$). **Conclusion:** Our results indicate that depression or depressive symptoms may be used to predict CF in people post-stroke.

4.2 Introduction

Post-Stroke Fatigue (PSF) is a prevalent issue experienced by as many as 76% of people post-stroke.[123] PSF manifestation can become a chronic issue[124] that affects performance of daily activities[18] and leads to poor quality of life.[66] However, not many studies recognized the unique nature of chronic fatigue (CF) as part of the PSF constructs and its impact on stroke rehabilitation effort.

The North American Nursing Diagnosis Association (NANDA) has defined fatigue as “an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work.”[42] In addition, fatigue has also been defined as a feeling of early exhaustion, weariness, lack of energy and aversion to effort.[17] However, none of these definitions clearly differentiates different types of fatigue which consisted of different dimensions.

A general classification of the fatigue dimensions includes perception, physiological, biochemical, and behavioral.[32] In 1993, Piper described a dichotomy fatigue theory, which classifies fatigue as either acute or chronic. It was proposed that the key differentiating factors between acute and chronic are duration, onset of fatigue, and the recovery rate.[53] Fatigue can be associated with exertion such as exercise, household activities, or social activities.[55] Researchers have distinguished the type of fatigue as “exertion fatigue” (EF). EF is acute in nature with a rapid onset, short duration, and short recovery period, and is commonly experienced after exertion of physical power or use of mental effort.[53, 55, 56] On the other hand, “chronic fatigue” (CF) is defined as a state of weariness unrelated to previous levels of exertion, and is associated with pathological factors.[53, 56] The difference between EF and CF is that CF does not necessarily have a relationship with the performing of activities, while EF is directly related to activities.[36] Due to the close association between CF and underlying medical conditions,[28] the impact and ramification of CF cannot be neglected.

What exactly is CF? The previous consensus is that fatigue that persists 6 months or longer can be considered as CF.[28, 133] The cause of CF is uncertain; several factors have been considered to contribute to CF such as depressive symptoms,[14, 58-60] cancer related treatments,[35, 57, 134] and medication side-effects.[35] In people post-stroke, researchers have proposed several potential contributing factors specific to PSF.[20] Multiple factors could contribute to PSF such as deconditioning, physical impairment, disuse, sleep disorders, medication side effects, and depression. However, it was unclear which factors contribute to different types of PSF. In the present study, three variables were considered key contributors to CF to examine the PSF issue in people post-stroke – depression,[11, 14-16, 20] aerobic fitness,[18, 20, 65] and physical impairment.[14, 15, 20, 65]

To date, depression is considered the most influential factor associating with CF in primary care[40] and is the only identified factor with a significant relation to PSF.[14, 17, 59] In people post-stroke, researchers have suggested that depression and depressive symptoms should be considered or controlled[66] while acknowledging other factors may also play a role in contributing PSF.[64] Interestingly, fatigue has been found to exist independently of depression in survivors of stroke.[11, 14-16] In

2005, Choi-Kwan and colleagues conducted a mail-survey study in 220 people post-stroke to evaluate the characteristics of and the factors associated with PSF.[16] They reported that 57% of people post-stroke reported fatigue problems, while 24% of which also reported depression complaint. The authors concluded that fatigue is a prevalent issue among survivors of stroke; and fatigue can exist independently of depression. In the present study, depression was assessed as a potential predictor of CF using the Geriatric Depression Scale (GDS).[74]

Previous research has revealed that aerobic fitness is reduced by approximately 50% in people post-stroke;[10, 45, 77, 79] a comparable reduction was reported in ambulatory capability by conducting a six-minute-walk test.[78, 80] In 2006, Michael and colleagues investigated how aerobic fitness, mobility deficit, ambulatory activity, self-efficacy for falls, and social support are related to chronic fatigue in 53 people post-stroke.[65] Their finding did not show a direct association between aerobic fitness and fatigue, which conflicts with what previous researchers have suggested.[18, 20] In addition, a recent exercise intervention study in people with CFS suggests that a six-month aerobic training improved both physical and psychosocial dimensions of chronic fatigue.[135] Therefore, further investigation is needed to determine the true role of aerobic fitness in CF in people post-stroke. In this study, VO_{2peak} was assessed as a potential predictor of CF using a maximal effort graded exercise test on a total body recumbent stepper.[83]

Although it has previously been suggested that CF may not be related to muscle fatigability;[133] researchers who examined fatigue in people post-stroke have considered physical impairment as a potential contributing factor to PSF.[14, 16, 20, 65, 66] Survivors of stroke often experience the increased energy expenditure due to limitations such as limited range of motion, muscle tone, mal-alignment, and other musculoskeletal problems, which lead to poor biomechanical efficiency (e.g. inadequate gait due to the inability to activate normal motor patterns).[78] In a 2006 study that examined pain and fatigue, patient characteristics, stroke type, stroke severity, stroke risk factors, and fatigue were assessed in 253 people post-stroke at baseline and 1 year post-stroke.[71] Fatigue was assessed by asking the subjects whether they had experienced fatigue which had started after the stroke. After 1 year, survivors were examined with respect to residual impairment, disability, cognition and depression. This study reported that fatigue was associated with physical disability and sleep disturbances. In this study the level of motor control was reflected by the FM total motor score (FMTM), which consisted of the combined scores from the upper extremity (UE) and the lower extremity (LE) portions of the FM test.[93]

To date, the potential contributing factors of CF following stroke remain undetermined. To the author's best knowledge, no study has yet identified predictors of CF in people post-stroke using quantifiable outcome measures as predictors. The present study aimed to identify the potential contributing factors of CF in people post-stroke using multiple linear regression where the response variable are CF measures (measured by FSS and $VAFS_{at\_rest}$); and the explanatory variables are depressive symptoms (measured by GDS), aerobic fitness (measured by VO_{2peak}), and motor control (measured by FMTM).

4.3 Methods

Experimental Design

This study used a convenience sample and a cross-sectional design to determine the predictors of CF in people post-stroke using depressive symptoms, aerobic fitness, and motor control as potential contributing factors.

Participants

Twelve men and 9 women (59.5 ± 10.3 years, 4.1 ± 3.5 years post-stroke) participated in the study. Individuals were recruited from local stroke support groups and the ASTRA (Advancing Stroke Treatment through Research Alliances) participant database. To be included in this study, all participants must: 1) have a diagnosis of stroke ≥ 6 months and ≤ 5 years ago, 2) have the ability to perform the exercise movement on a total body recumbent stepper, 3) receive medical clearance from their primary care physician to confirm that subject is medically stable and able to participate in exercise, and 4) score < 2 on a dementia screening tool, the AD8.[114, 115] Subjects were excluded from the study if they presented with any of the following:

- Hospitalization for myocardial infarction, heart surgery, or congestive heart failure during the preceding 3 months.

- Recent symptoms of chest discomfort.
- Resting blood pressure of 160/100 or greater.
- Currently using a pacemaker.
- Currently smoking or significant pulmonary pathology.
- Alcoholism or alcohol dependency.
- Recreational drug use.
- Medication change within the duration of the study (e.g. antidepressants, cardiac medications).

The Human Subjects Committee at the University of Kansas Medical Center approved the study. Institutionally approved informed consent was obtained in writing prior to participation in the study.

Procedure

The experiment consisted of 2 visits. One visit involved assessment of chronic fatigue, level of motor control, and depressive symptoms. The other visit involved an assessment of the peak oxygen uptake using a calibrated total body recumbent stepper (NuStep, Inc; 5111 Venture Drive Suite 1, Ann Arbor, MI 48108). The 2 visits were scheduled 24-48 hours apart to allow recovery.

Variables

Fatigue Assessment. Chronic Fatigue (CF) was measured by the Fatigue Severity Scale (FSS) and the Visual Analog Fatigue Scale (VAFS). The FSS is a 9-item scale that has been shown to be reliable and valid to assess fatigue level over the previous week.[34] The VAFS consists of possible score ranges from 0 to 100, measured in millimeters on a 10cm vertical line using a pen. It was administered to assess subject's level of fatigue at rest ($VAFS_{at\_rest}$). The score was obtained by measuring the line from "No Fatigue" to the point indicated by the subject that represents their fatigue level. The VAFS has been reported to be a good reliability, responsiveness, and validity to assess fatigue in people post-stroke (Chapter 2).

Geriatric Depression Scale (GDS). The GDS is a questionnaire that includes 30 items that refer to affective, cognitive, and behavioral symptoms of depression to assess mood. It has been tested and used extensively with the older population with good validity and reliability.[74, 125] The possible score ranges from 0 to 30.

Aerobic Fitness (VO_{2peak}). To assess aerobic fitness, a maximal effort graded exercise test was conducted using a calibrated metabolic cart and the mTBRS-XT protocol our lab has developed specifically for people post-stroke.[83] Subjects were asked to refrain from eating food for an hour and drinking caffeine for 2 hours prior to the test. According to the test protocol, subjects stepped at 80 steps-per-minute (SPM) with a gradually increasing level of resistance. A cool-down period of 4 minutes followed the end of the test. Each subject's ECG was monitored by a 12-lead

ECG system during the exercise test. The exercise test was terminated using the following criteria: (1) the participant reached volitional fatigue and requested to end the test, (2) the participant's VO_{2peak} plateaued or decreased despite continuation of exercise, (3) the participant was unable to maintain the cadence, or (4) an adverse cardiovascular event or response to the exercise test was observed. The successful completion of the maximal effort graded exercise test (measured in VO_{2max}) was determined by reaching 1) the predicted maximal heart rate [(220-age), and 2) the respiratory exchange ratio (RER > 1.1), and 3) plateau of VO_2 values despite continuation of exercise.[118] When the subjects were unable to achieve their maximal effort, the aerobic fitness level at the peak values were collected (measured in VO_{2peak}).

Fugl-Meyer (FM). The FM was used to determine the level of motor function in the hemiparetic limbs following stroke. The FM is a reliable and valid tool that was specifically designed as a clinical measure of sensorimotor impairment for stroke.[93] The total possible score is 124, which consists of sensation (FMSEN - 24), upper extremity (FMUE - 66), and lower extremity (FMLE - 34). Because the fatigue-inducing exercise in this study required motor performance of all four limbs, the combined total motor (FMTM) scores of the FMUE and FMLE were determined (FMTM = FMUE + FMLE)[95] and used for analyses.

Data Analysis

SPSS 16.0 (SPSS, Inc; 233 S. Wacker Drive 11th Floor Chicago, IL 60606) statistical software was used to perform all statistical analysis. Descriptive statistics were calculated; correlations among variables were calculated with the Pearson correlation coefficient. Histograms for each variable were analyzed for normal distributions, and scatterplots were analyzed for outlying scores. Stepwise multiple regression models with 3 predictors (GDS score, VO_{2peak}, and FMTM score) were calculated for chronic fatigue (CF), where the response variables were FSS and $VAFS_{at\_rest}$ scores. The validity of each model was assessed through analysis of colinearity statistics (variance inflation factor) and Q-Q plots of unstandardized residuals.

Independent t-test was performed to determine differences in fatigue and GDS measures between male and female. In addition, five secondary factors – sex, stroke lesion side (i.e. left, right), stroke subtype (i.e. ischemic, hemorrhagic), sleep apnea (i.e. sleep apnea, no sleep apnea), sleep medication (i.e. medication, no medication), depression medication (i.e. anti-depressant, no anti-depressant) were documented to obtain descriptive data. In addition, we also explored the relationship between CF and other variables from this body of work using the Pearson correlation coefficient, more specifically, exertion fatigue (EF), recovery rate (RR), and $VAFS_{at\text{-}rest}$ (Chapter 3). A 0.05 level of significance was used for all statistical tests.

Sample Size

Initially, it was proposed that 30 subjects with chronic stroke will be recruited. In order to maximize limited resources and to avoid over-recruitment of subjects, a planned interim analysis was conducted after the completion of data collection for 20 subjects. The goal of this analysis was to determine whether further recruitment is required in order to satisfy statistical significance. To reduce the chance of making a type I error, alpha level was set at 0.01 for the interim analysis.

Power calculations indicated that for the interim analysis, the twenty subjects had 70% power to detect explanatory variables in a multiple linear regression (with three explanatory variables) with an R-square of 0.27 or greater and have 80% power to detect explanatory variables with an R-square of 0.31 or greater. These calculations used were done at the alpha = 0.01 level, as we conducted an interim analysis after twenty subjects (nQuery Advisor 6.01, 1995-2005).

4.4 Results

Data was collected from twenty-one individuals with chronic stroke. Subject characteristics and descriptive data of secondary factors are shown in Table 4.1; descriptive statistics of all variables are shown in Table 4.2. Using Pearson's correlation coefficient, significant correlations were found for FSS and GDS ($r = 0.639$; $p = 0.002$), and for $VAFS_{at\_rest}$ and GDS ($r = 0.980$; $p < 0.001$), as shown in Figure 4.1 and 4.2. The complete results of correlation among variables are shown in Table 4.3.

Using stepwise multiple regression, we found the regression models for the CF with 2 response variables (FSS and $VAFS_{at\_rest}$) and 3 explanatory variables (GDS score, VO_{2peak}, and FMTM score) were statistically significant. GDS score was found to be a significant individual factor that explained 37.8% of variance in CF when using the FFS as the fatigue measure; and 95.8% of variance in CF when using the $VAFS_{at\_rest}$ as the fatigue measure. The results of these models are presented in Table 4.4.

Using independent t-test, significant differences were found between male and female in terms of FSS, $VAFS_{at\_rest}$, and GDS scores as indicated in Table 4.5. Lastly, we did not find any relationship for CF and EF ($r = 0.329$; $p = 0.145$) or for CF and RR ($r = -0.132$; $p = 0.567$), but a significant positive correlation for CF and $VAFS_{at\text{-}rest}$ ($r = -0.752$; $p < 0.001$),

4.5 Discussion

Although both of our regression models suggest that depression is an independent predictor of CF, the variance explained in each model differs due to different response variables used to represent CF; and the results should be interpreted with caution. In the model where CF was represented by the VAFS, fatigue was measured in real time (i.e. at rest). Although it was unrelated to exertion level and it appeared to be persistent on separate days, its nature may be different from the type of fatigue measured by the FSS. The type of fatigue measured by the VAFS at rest could be viewed as “baseline fatigue” and may be more related to 24-

hour sleep and wake cycles also known as the circadian cycle. As previously discussed (Chapter 2), we found evidence of baseline fatigue in most subjects (20 out of 21) at rest prior to fatigue-inducing exercise using the VAFS. This discovery indicates that this type of baseline fatigue can exist independently of physical stress, which is persistent and chronic in nature and may explain the strong relationship with the CF score measured by the FSS. One possible explanation may the testing time of the day in this study. In order to capture fatigue, we asked subject to participate the testing sessions in the afternoon. It is possible that the $VAFS_{at\_rest}$ captured a type of fatigue that is sensitive to activity and rest cycle during the day (possibly circadian fatigue). However, this study was not designed to identify or differentiate circadian fatigue. Future study is needed in order to investigate the nature of baseline fatigue detected by the VAFS and its association with circadian cycle (e.g. change in fatigue level through time).

On the other hand, although less variance was explained using FSS as the response variable in the regression model, FSS was designed to capture fatigue level experienced over a 2-week period, which was chronic in nature and perhaps more appropriately describing CF in people post-stroke. An FSS score ≥ 4 has been considered fatigued in people with multiple sclerosis.[34] In our study, the average FSS score was 4.2 ± 1.7, similar to scores documented in previous fatigue studies in people post-stroke ($4.1 \pm 1.3 \sim 4.7 \pm 1.3$).[64, 66] These results suggest the possibility that people post-stroke may be more likely to experience chronic fatigue.

Our results confirm with previous studies[11, 14] and suggest that depression is a significant factor relating to fatigue in people post-stroke. Post-stroke depression (PSD) is defined as depression occurring after a cerebrovascular accident and is the most frequent psychiatric complication of stroke.[136] Many symptoms that are commonly experienced after stroke such as cognitive impairment, aphasia, functional impairment, and social isolation are also viewed as risk factors to PSD;[137] which may explain the close association between stroke and depression. Although the pathophysiology of PSD is still debated, researchers have proposed various hypotheses. Some proposed a biological hypothesis that suggests the impact of stroke on neural circuits involved in mood regulations and found correlations between PSD and right hemisphere stroke;[138] while others suggested that social and psychosocial stressors associated with stroke are primary causes of PSD.[137] Although there's no solid evidence to support these hypotheses, the relationship between depression and stroke cannot be denied.

In 1999, Ingles and colleagues conducted a survey study in a community setting in order to investigate the frequency and outcome of fatigue, its impact on functioning, and its relationship with depression in people post-stroke.[11] They administered the self-reported Fatigue Impact Scale (FIS) that measures the presence and severity of fatigue and its impact on cognitive, physical, and psychosocial functions to 181 people post-stroke. In addition, they also administered the Geriatric Depression Scale (GDS) to measure the severity of depressive symptoms as did in our study. Out of the 88 participants who met the criteria and participated, they found that 68% of participants reported fatigue problems, while 40% of which were depressed.

In 2001, Van der Werf and colleagues conducted a survey study to assess the relationship between PSF and depression and levels of physical impairment.[14] Fatigue was measured using the Checklist Individual Strength (CIS); while depression was measured by the Beck Depression Inventory for Primary Care (BDI-PC). The CIS is a 20-item self-report questionnaire that captures four dimensions of fatigue (i.e. subjective experience, reduction in motivation, reduction in activity, and reduction in concentration).[75] They found that 20% of people post-stroke reported elevated depression scores; and that depression explained 11% of the variance in fatigue; while our regression models indicated that depression explained 37.8% of variance in CF. Both the FSS and the CIS are questionnaire-based measures that evaluate fatigue over a 2-week period. However, the dimensions of the CIS characterize depression as well as fatigue symptoms, which may be confounding. It is unknown if the CIS can differentiate depression from fatigue. In addition, BDI-PC used to measure depression in the previous study is a short screening scale that consists of seven items and produces only a binary outcome of "not depressed" or "depressed" for patients above a cutoff score of 4.[139] Compare to the BDI-PC, the GDS consists of 30 items and meaures the severity of depressive symptoms with a continous score, not outcome dignosis with a cutoff score. These differences could also contribute to the discrepency in finding between the previosu and present study.

Nevetheless, the association between depression and fatigue can be agreed by literature in general.

It is important to acknowledge that depression does not explain the variance in CF exclusively according to our models. In our study, although the CF score (measured by the FSS) showed significantly moderate correlation with the GDS score, these two questionnaires each possess unique items which measure distinctive psychometric qualities of subjects (Appendix II & III, respectively). PSF is a multifactorial phenomena that involves both physiological and psychosocial properties;[65] and researchers have suggested that fatigue can exist independently of depression.[11, 16] According to Portenoy's integrated fatigue model,[52] CF can be closely associated with factors that are either physiologic (e.g. chronic pain) or psychosocial (e.g. depression). Chronic pain, systemic disease, medical treatment side effects, and sleep disorders-related sleep deprivation could contribute to chronic fatigue in people post-stroke. Although we collected information regarding stroke lesion side, stroke subtype, sleep apnea, sleep medication, and depression medication, we did not have sufficient numbers of sample to perform subgroup analyses.

It has been previous established that pain or discomfort symptoms are more frequently reported by women as compared to men.[140] Our secondary analysis revealed that female survivors of stroke have a significantly higher level of CF than male counterparts as illustrated in Figure 4.1. Similar finding regarding fatigue and gender differences was found in a different clinical population.[141] In 2008, Cain and colleagues conducted an investigation that compared gender differences in people with irritable bowel syndrome (IBS)[141] and found that female participants (both pre-menopausal and post-menopausal) reported significantly more joint and muscle pain, stress, and fatigue than male. Furthermore, this effect was found stronger in post-menopausal women than pre-menopausal women, which suggested a possible relationship between biologic factors (e.g., sex hormones) and gender-related differences in clinical populations. In addition, we also found significantly higher depression scores in female survivors of stroke than male as previous studies suggested.[142-144] Depression after stroke can be detrimental as it has been associated with an increased risk of suicide in female survivors of stroke.[145] In a 2001 study that investigated the frequency of depression in people several years after stroke;[144] ninety-nine survivors of stroke were examined at baseline and 7 years later. The study found that the frequency of depression in female survivors of stroke was significantly higher than male. Figure 4.1 indicates a cluster of female subject who reported higher depression as well as fatigue.

It has been well documented that women consistently report greater numbers of physical symptoms more frequently than men.[146] Theories to account for this gender difference include physiological, sociocultural, and psychological.[140, 146] In 1994, Kroenke and colleagues conducted a study to assess gender differences for specific symptoms in 1000 patients from four primary case sites and assessed how much of these differences were attributable to psychiatric comorbidity.[140] The effect of gender on symptom reporting was assessed by multivariate analysis, adjusting for depressive and anxiety disorders as well as age, race, education, and medical comorbidity. They fund almost all symptoms were reported more commonly by women, especially physically unexplained symptoms; and gender was determined the most important demographic factor associated with symptom reporting, followed by education. The authors concluded that most physical symptoms are typically reported at least 50% more often by women than by men; and gender influences symptom reporting in patients independent of psychiatric comorbidity.[140]

Lastly, CF has also been attributed to chronic pain,[52] a commonly experienced symptom in people post-stroke.[147, 148] However, pain was not assessed in the present study. Future studies should consider sex differences and explore additional factors (e.g. pain) that may potentially contribute to chronic fatigue in people post-stroke.

4.6 Conclusion

We found that depression is an independent predictor of chronic fatigue (CF) in people post-stroke. In addition, our data also suggests that female survivors of stroke have a significantly higher level of fatigue and depression than males. PSF is prevalent and can have severe negative impacts in people post-stroke; it is crucial to acknowledge that CF is a unique construct of PSF that differs from other types of fatigue that are exertion-related and acute in nature. Before individualized therapeutic treatment can be implemented, clinicians must be able to identify the nature of fatigue and its contributing factors in people post-stroke.

Figure 4.1 Scatterplot illustrating the relationship between FSS and GDS scores.
CF – Chronic Fatigue score (measured by the Fatigue Severity Scale)
GDS – Geriatric Depression Scale
0 – Female
1 – Male

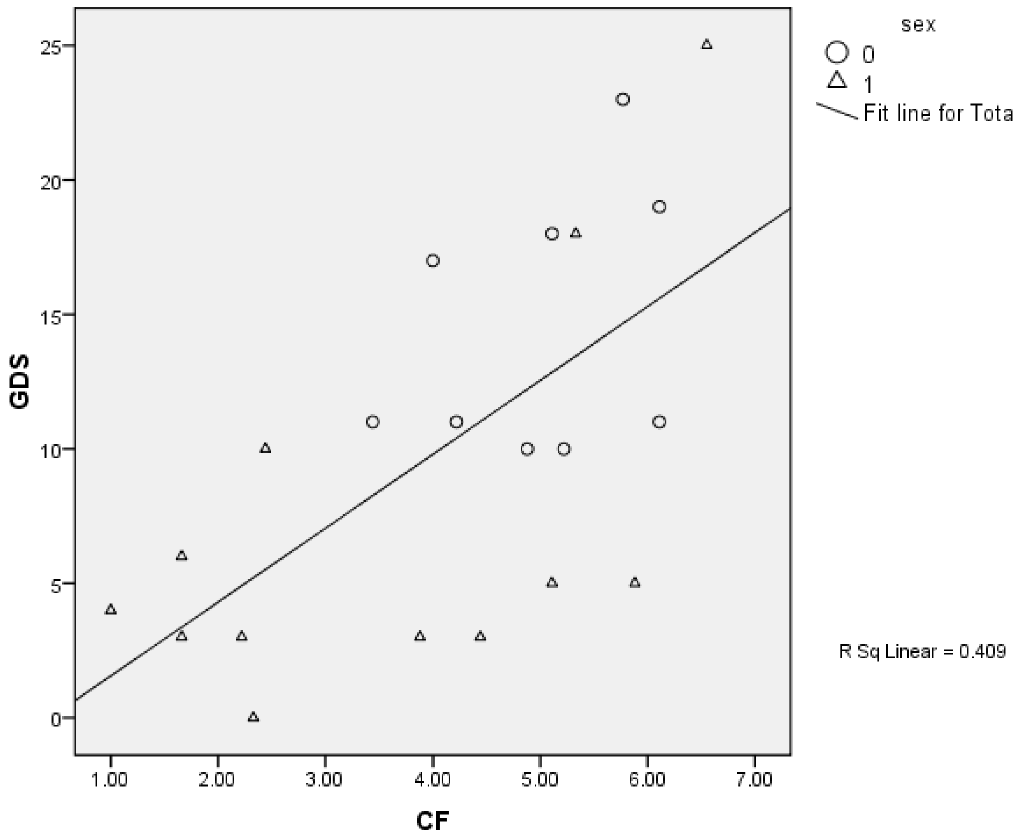


Figure 4.2 Scatterplot illustrating the relationship between $VAFS_{at\_rest}$ and GDS scores.
$VAFS_{at\_rest}$ – Visual Analog Fatigue Scale at rest
GDS – Geriatric Depression Scale

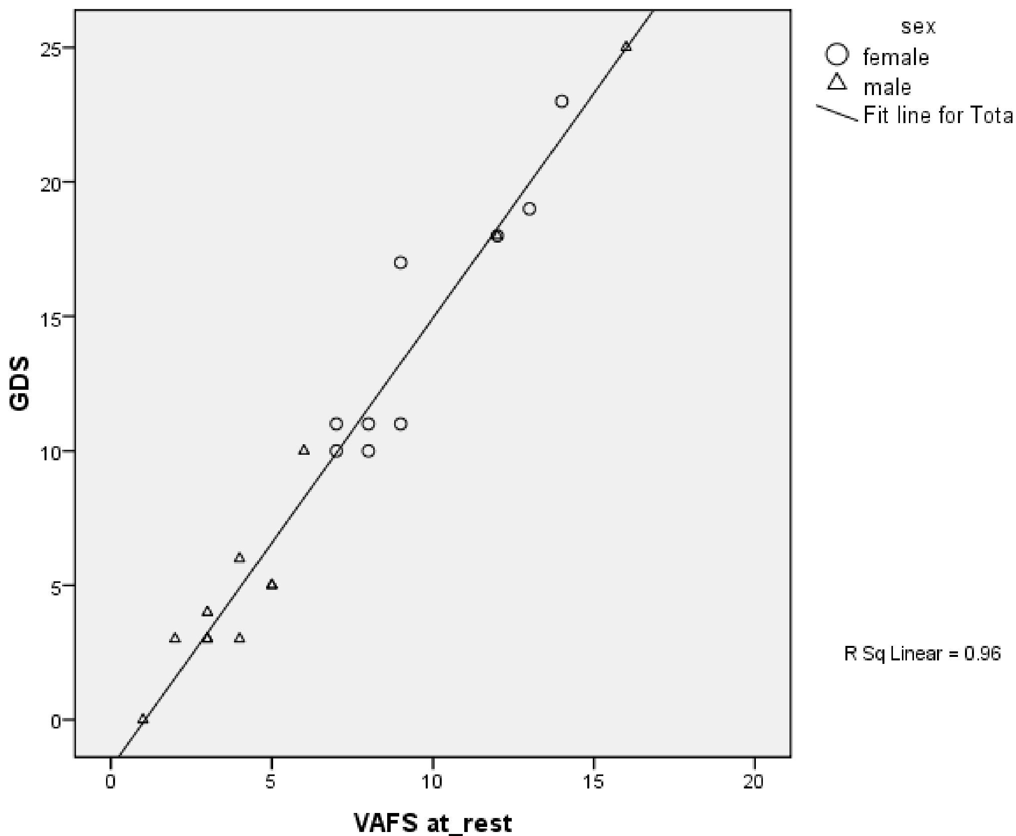


Table 4.1 Participant characteristics (n = 21). Values are means $\pm$ SD.

Characteristics	***Values***
Men / women	12 / 9
Age (years)	59.5 ± 10.3
Time post-stroke (years)	4.1 ± 3.5
Stroke lesion side: right / left / brain stem	15 / 4 / 2
Stroke subtype: ischemic / hemorrhagic	18 / 3
Sleep apnea: yes / no	9/12
Sleep medication: yes / no	4/17
Depression medication: yes /no	9/12

Table 4.2 Outcome measures (n = 21). Values are means ± SD.

Outcome Measures	**Values**
Response Variables	
FSS	4.2 ± 1.7
$VAFS_{at\_rest}$	7.2 ± 4.3
Explanatory Variables	
GDS	10.2 ± 7.3
VO_{2peak} (ml/kg/min)	16.2 ± 6.5
FMTM	70.8 ± 28.8

FSS – Fatigue Severity Scale
$VAFS_{at\_rest}$ – Visual Analog Fatigue Scale at rest
GDS – Geriatric Depression Scale
VO_{2peak} – Peak Oxygen Uptake
FMTM – Fugl-Meyer Total Motor

Table 4.3 Pearson correlation among variables.

Variable	FSS	$VAFS_{at\text{-}rest}$	GDS Score	VO_{2peak}	FMTM Score
FSS	1.000				
$VAFS_{at\ rest}$	**.752	1.000			
GDS Score	**.639	**.980	1.000		
VO_{2peak} (ml/kg/min)	-.125	-.065	-.057	1.000	
FMTM Score	.142	.149	.159	.404	1.000

**. Correlation is significant at the 0.01 level (2-tailed).

FSS – Fatigue Severity Scale
$VAFS_{at\_rest}$ – Visual Analog Fatigue Scale at rest
VO_{2peak} – Peak Oxygen Uptake
FMTM – Fugl-Meyer Total Motor
GDS – Geriatric Depression Scale

Table 4.4 Linear regression model for CF measures.

Regression Model with FSS as Response Variable	
Adjusted R^2	0.378
F	13.130
P	0.002

Explanatory Variables	**B**	***P***
GDS	*0.149*	*0.002*
VO_{2peak}	-0.089	0.628
FMTM	0.041	0.824

Regression Model with *$VAFS_{at\_rest}$* as Response Variable	
Adjusted R^2	0.958
F	459.717
P	< 0.001

Explanatory Variables	**B**	***P***
GDS	*0.574*	*< 0.001*
VO_{2peak}	-0.009	0.848
FMTM	-0.007	0.882

FSS – Fatigue Severity Scale
$VAFS_{at\_rest}$ – Visual Analog Fatigue Scale at rest
GDS – Geriatric Depression Scale
VO_{2peak} – Peak Oxygen Uptake
FMTM – Fugl-Meyer Total Motor
P – Probability Values
B – Weights

Table 4.5 Sex differences in fatigue and depression measures.

Variable	Sig. (2-tailed)	Sex	n	Mean	SD
FSS	0.050	Female	9	4.9844	.94683
		Male	12	3.5417	1.88456
$VAFS_{at\_rest}$	0.016	Female	9	9.67	2.646
		Male	12	5.33	4.355
GDS	0.017	Female	9	14.44	4.851
		Male	12	7.08	7.292

n – Subject Number
SD – Standard Deviation
FSS – Fatigue Severity Scale
$VAFS_{at\_rest}$ – Visual Analog Fatigue Scale at rest
GDS – Geriatric Depression Scale

Chapter 5

Discussion and Conclusions

5.1 Summary of Findings

The work presented here was undertaken to help characterize the nature of post-stroke fatigue (PSF). Specifically, this research fills the void in the literature by establishing a reliable fatigue assessment and distinguishing two distinct types of fatigue each with its key contributing factor in people post-stroke. The findings presented suggest that different factors could contribute to different types of fatigue; differentiated findings such as these are important both to validate theoretical models of post-stroke fatigue and to guide rehabilitation practice. Through this work and the follow-up studies beyond, it is hoped that a better understanding will be gained of the challenges faced by those who experience post-stroke fatigue.

Chapter 2. Reliability, Responsiveness, and Validity of the Visual Analog Fatigue Scale to Measure Exertion Fatigue in People with Chronic Stroke

Assessing PSF is difficult due to its subjective nature and the ambiguity of what's being measured. In addition, although many questionnaires and scales are available in the literature, none attempts to distinguish exertion fatigue (EF) from chronic fatigue (CF) using physiologic measures, nor was any specifically designed for survivors of stroke. In an attempt to resolve this issue, we developed the Visual Analog Fatigue Scale (VAFS) and conducted experiments to test its effectiveness.

The focus of Chapter 2 was to determine the reliability, responsiveness, and validity of the VAFS to assess PSF in people with chronic stroke. We designed a 2-visit experiment with 14 days between visits. The first visit involved a fatigue-inducing exercise and VAFS at 3 different time points (i.e. at rest, post-exercise, post-recovery). Physiologic measures were recorded during exercise (i.e. heart rate and blood pressure). A second visit was scheduled 14 days after the first visit with identical testing procedures. The results suggested good intra-rater reliability for the VAFS measures taken during the 2 separate sessions and a strong relationship for between the VAFS and physiologic measures. It was determined that the VAFS was a reliable and valid tool to measure fatigue level at all time points and was sensitive to fatigue change due to exercise. Therefore, the VAFS was utilized to measure both EF and CF.

Chapter 3. Predictors of Exertion Fatigue in People Post-Stroke

To identify the potential contributing factors of EF in people post-stroke, we used multiple linear regression analysis where the response variable was EF and the explanatory variables were aerobic fitness (measured by VO_{2peak}), motor control (measured by FMTM), and depressive symptoms (measured by GDS). Data was obtained from the first visit. Using stepwise linear regression, the results revealed that the regression model for the EF with 3 variables (VO_{2peak}, FMTM, and GDS scores) was statistically significant, while VO_{2peak} was a significant individual factor that explained 30.5% of variance in EF. Therefore, these results suggested that aerobic fitness is a key contributing factor to EF in people post-stroke.

Chapter 4. Predictors of Chronic Fatigue in People Post-Stroke

The focus of Chapter 4 was to identify the potential contributing factors of CF in people post-stroke. We used a parallel model similar to analysis used in Chapter 3 to carry out multiple linear regression analysis where the response variable was CF and the explanatory variables were aerobic fitness (measured by VO_{2peak}), motor control (measured by FMTM), and depressive symptoms (measured by GDS). Data was obtained from the first visit. Using stepwise linear regression, we found that the regression model for the CF with 3 variables (VO_{2peak}, FMTM, and GDS scores) was statistically significant, while GDS was a significant individual factor that explained up to 37.8% of variance in CF. Therefore, these results suggestd that depression is a major contributing factor to CF in people with chronic stroke.

5.2 Possible Mechanisms for Post-Stroke Fatigue

Exertion Fatigue

In the present body of work, it was found that aerobic fitness is the key contributing factor to EF (Chapter 3). It has been suggested that any factor that interferes with the ability to maintain adequate oxygen levels in the blood can lead to fatigue.[32] More specifically, the decrease of hematocrit values and hemoglobin counts may contribute to O2 deficit and lead to fatigue. A recent study has identified hemoglobin as one of the biomarkers to explain possible fatigue mechanisms in women with breast cancer who received chemotherapy.[149] The authors further suggested that measurement of serum bilirubin can be considered as a potential marker by evaluating hepatobiliary and enthropoietic function of red blood cells for future fatigue studies.

In addition, accumulation of several metabolites has been associated with fatigue.[51] In people post-stroke, the decrease of aerobic fitness and the accumulation of lactate acid is a likely mechanism for PSF. It is well-known that repetitive muscle activities can produce an accumulation of lactic acid, which can cause the muscle fiber contraction force to decrease.[150] During anaerobic activities (e.g. lifting of heavy household objects) or the anaerobic phase of exercise (e.g. first few minutes of jogging), when the rate of demand for energy is high, lactate is produced faster than the ability of the tissues to remove it and concentration level begins to rise. This is less a concern in the healthy population because the increased lactate can be removed via a metabolic pathway known as the Krebs cycle, which refers to the oxidation of lactate to pyruvate by oxygenated muscle fibers (Type-I fibers) then used as fuel.[150] However, in people post-stroke, the efficiency of this metabolic pathway may be hampered by the reduction of aerobic fitness capacity (or lack of Type-I fibers), which can exacerbate the accumulation of lactic acid beyond normal level and lead to delayed recovery. In this body of work, we found a positive relationship between aerobic fitness and recovery rate (RR); and a negative relationship between EF and RR. In other words, the better the aerobic fitness, the better the recovery after exercise; and the better the recovery, the lesser the fatigue experienced after exercise. The literature has shown that people post-stroke can benefit from aerobic exercise training in order to achieve a healthier lifestyle.[10, 77, 78, 84] However, more work is needed in order to determine the exact role of aerobic fitness in PSF mechanisms. Future study may consider examining the effect of exercise intervention on hematocrit values, hemoglobin counts, serum bilirubin, and lactic acid accumulation.

Chronic Fatigue

In agreement with previous studies that suggest a relationship between depression and fatigue in people post-stroke,[11, 14, 16] we found that depression was a significantly predictor of CF in the present body of work (Chapter 4). Although the underlying pathophysiology of depression is still debated, MacHale and colleagues have suggested the impact of stroke on mood regulation may be the cause of PSD in people post-stroke.[138] In addition, Payne et al proposed a biochemical pathway in a recent cancer care study that may help explain the association between depression and fatigue.[51]

Depressive symptoms and fatigue are believed to be connected via a neuroendocrine transmitter pathway.[149, 151] The neuroendocrine system, specifically the hypothalamic-pituitary-adrenal (HPA) axis, may influence level of fatigue and depressive mood.[51] The HPA axis is a complex set of interactions among the hypothalamus, the pituitary gland, and the adrenal gland, which constitute a major part of the neuroendocrine system that controls reactions to stress and regulates body processes such as mood, emotions, sexuality, digestion, immune system, and energy storage and expenditure. The underlying mecahnism of fatigue and depression may attrribute to the dysregulation of HPA,[152] which can influence the production levels of serotonin and melatonin.[149, 151] In addition, sex difference could also contribute to CF as women are more likely to experience depression and fatigue.[140] Biologic factors such as sex hormones[141] may play a role in hormonal and mood regulation.

It is important to acknowledge that serotonin and melatonin are important regulators of the 24-hour sleep and wake cycles also known as the circadian cycle.[153] Melatonin production is sensitive to light intensity; more specifically, melatonin secretion is inhibited by light and promoted by darkness.[153] Therefore, an individual's natural wake and sleep cycle corresponds with melatonin production. A previous study has identified melatonin as a possible biomarker to explain fatigue mechanisms in women with breast cancer.[149] Payne and colleagues observed increased daytime melatonin levels over three months during chemotherapy, which suggested elevated fatigue intensity experienced by subjects. Therefore, it is important to consider the link among depression, fatigue, serotonin and melatonin because serotonin may be an indicator of depression and is a precursor to melatonin.[51]

Derived from the biochemical dimension of Piper's fatigue model,[32] Payne's neuroendocrine theory offered a plausible explanation to address the relationship between depression and fatigue from a physiologic perspective.[51] Although it is unknown whether this neuroendocrine pathway can be applied in other clinical populations such stroke, it provided a valuable conceptual framework for future research.

Although our findings show that EF and CF each has a different predictor, it is important to acknowledge EF and CF may co-exist or overlap in people post-stroke as

PSF is multidimensional. Specifically, survivors of stroke who experience multiple symptoms (e.g. lower aerobic fitness and depression) could experience both EF and CF throughout daily activities. EF and CF may also share other potential factors that are yet recognized; further investigation is needed in order to identify additional contributing factors of PSF.

5.3 Limitations

Assessing VO_2

Obtaining VO_{2peak} in people post-stroke has been a challenging throughout literature due to physical limitations in people post-stroke such as muscle tone, limited range of motion, hemiparesis, poor postural control, and poor coordination. Nevertheless, all participants in this presented work were able to participate in the maximal effort graded exercise test using the mTBRS-XT protocol.[83] In our study, 5 out of 21 subjects were able to reach their maximal effort; while the other 16 subjects reached their peak effort according to our study criteria. The 5 subjects who reached maximal oxygen uptake had VO_2 values that ranged from 19.0 ml/kg/min to 33.1 ml/kg/min, which were higher than the group mean of 16.2 ml/kg/min. If we were able to obtain VO_{2max} from all subjects, it is hypothesized that VO_{2max} would strengthen the inverse relationship found between EF and aerobic fitness in the EF regression model. However, since VO_{2peak} is an underestimation of the actual maximal values, the results should be interpreted with caution as only 24% our subjects reached their maximal aerobic fitness capacity.

Physical Impairment

Motor control was not found predictive to either EF or CF model in the present body of work (Chapter 3 & 4). On possible explanation is that although our fatigue-inducing protocol involved all 4 limbs, it did not challenge subject's motor control ability at the highest level as it was performed on a non-weight-bearing instrument (i.e. TBRS). In a previous PSF study where the fatigue-inducing protocol involved a distance walk, motor control was found to be a significant predictor of EF.[154] These conflicting findings suggest that EF may be dependent of the type of activity involved and is task or performance-specific.

In people post-stroke, the hemiparetic limbs require significantly more energy to perform movement and result in increase of energy expenditure.[77, 78] This reduction of biomechanical efficiency can lead to unnecessary anaerobic glycolysis and may exacerbate lactate accumulation. More importantly, excessive hydrogen ions that are produced as lactate accumulates has also been associated with decrease of muscle force in healthy adults.[155, 156] Hydrogen ions can interfere with muscle excitability and impede muscle force by decreasing the number of calcium ions that are bound to troponin during excitation coupling. As the result, the number of actin-myosin contraction activity declines, thus decrease in total force output.[157]

Future studies may consider incorporating muscular strength measures (e.g. Biodex) when investigating the role of physical impairment in PSF mechanism. Although some researchers have used FM as an indicator of stroke severity or impairment;[95-97] muscle strength is a more direct measure of muscular properties and could perhaps aid explaining PSF in addition to motor control ability.

Sample Size

One of the limitations in this dissertation project is the small sample size. Although we were able to achieve statistical significance in our regression models, we were unable to perform subgroup analyses to determine group differences. Future study may consider a larger sample size to validate the EF and CF models, and to determine fatigue difference in people with different stroke subtypes and post-stroke time.

Visual Analogue Fatigue Scale

We were unable to establish normative values of the VAFS in healthy populations due to the limited sample size. We acknowledge the absence of these comparison values as a limitation. Future studies may consider assessing fatigue using the VAFS in both young and older healthy adults.

Lesion Location

Data on type of stroke and hemisphere were obtained based on subject's report. Type of stroke was classified as ischemic versus hemorrhagic; however, specific lesion location was not documented nor controlled for the present study. Although the relationship between right-hemispheric strokes and PSF has been suggested,[107] more studies have shown that lesion side and stroke subtype do not appear to contribute fatigue in people post-stroke.[11, 15-17] This matter remains at debate as the underlying mechanism between lesion location and fatigue has not been clarified. Given the limited sample size, we were unable to compare differences between groups based on stroke type due to limited sample size. Future study may consider control for lesion location and explore its relationship with PSF.

Medication

Individuals taking antidepressants, sleep agents, and ß-blockers were not excluded from participating in this study. Although the efficacy of antidepressants may alleviate some severity depressive symptoms, research suggests despite the prescription of antidepressants, depressive symptoms can persist in people post-stroke.[104] In addition, we acknowledge the side effects of sleep agents may have (e.g. drowsiness) on the severity of fatigue.

ß-blockers have been associated with increased risks of depressive symptoms, fatigue, dizziness, hypotension and sexual dysfunction. However, recent review studies[158, 159] suggest no significant increased risk of depressive symptoms and only small increased risks of fatigue and sexual dysfunction based on previous clinical trials data. Although medication was documented in the present study, we were unable to compare differences between groups due to limited sample size. Future studies with a larger sample size may consider control or screen for antidepressants, sleep agents, or ß-blockers.

Pain

Pain was not assessed in this body of work. Although de Groot and colleagued suggested that pain is one of the potential contributing factor to PSF,[20] pain is often overlooked.[71] Literature has shown a strong relationship between pain and fatigue in people undergoing cancer treatment.[160] In a study of 69 women with lung cancer, 41% of subjects who had fatigue complains were found to experience frequent pain. In addition, the severity of fatigue and pain were significantly correlated.[160]

In 2006, Appelros documented general characteristics, stroke type, stroke severity, and risk factors at baseline in 377 people post-stroke.[71] After 1 year, 253 subjects were evaluated in terms of residual impairment, disability, cognition, and depression. The results indicate that 11% had stroke-associated pain and 53% had post-stroke fatigue. Pain was associated with depression and degree of paresis at baseline; while fatigue was associated with physical disability. The authors concluded that it is important to recognize the presence of pain and fatigue after stroke due to the prevalence and potential negative impact on quality of life in people post-stroke. Although the authors also suggest the possible co-existence between depression with pain or fatigue, pain was not analyzed as a potential contributing factor to PSF, and its relationship with fatigue was also not determined. We acknowledge the influence pain may have on fatigue in people pos-stroke. Future studies should consider investigating pain as a contributing factor to PSF.

5.4 Clinical implications

With approximately 780,000 Americans experiencing stroke each year,[4] and many of which require extensive care,[5] it is the responsibility of health professional of all disciplines to help share the burden stroke's health consequences. The findings of the current research project may help clinicians treat people post-stroke.

Fatigue Classification

Assessment of post-stroke fatigue is challenging. The initial step of assessment should seek to identify the nature of fatigue (i.e. acute vs. chronic). Although there's no universal definition of fatigue, we suggest using onset, duration, and recovery rate as 3 differentiating criteria described in Piper's dichotomy fatigue model as illustrated in Figure 1.3. If exertion fatigue (EF) is suspected to manifest, the Visual Analog Fatigue Scale (VAFS) should be administered before and after a fatigue-inducing exercise (e.g. distance walk) to calculate the severity of EF ($EF = VAFS_{post\text{-}exercise} - VAFS_{at\text{-}rest}$). If chronic fatigue (CF) is suspected, the VAFS can be administered at rest to detect the level of CF in real-time. In addition, the Fatigue Severity Scale (FSS)[34] can also be implemented to detect CF.

Identification of Contributing Factors

The next step is to identify potential contributing factors. Besides aerobic fitness and depression that were identified in this body work as contributing factors for EF and CF, respectively, clinicians should also consider other potential contributing factors such as medication side effects, sleep disorders, and pain. In addition to the EF/CF parallel fatigue model as shown in Figure 5.1, we suggest the PSF-specific contributing factors described by de Groot as illustrated in Table 1.1.

Fatigue Management

Because PSF is multidimensional and multifactorial,[20] fatigue management options could be either pharmacological or non-pharmacological, nevertheless, it should always remain cause-specific. In other words, treatment effort should be made to counteract potential etiologies, if identifiable. These treatment options may include improvement of aerobic fitness, management of depression, treatment of sleep disorder, and elimination of nonessential drugs. Some of these options only pose minimal burdens to the individuals post-stroke and caregivers.

For people post-stroke who experience exertion fatigue (EF), increase of aerobic fitness is likely to improve the fatigue level experienced after exercise or vigorous activity. Researchers and health professionals have stressed the importance aerobic exercise and its related benefits;[77, 161] it has been shown to increase physiologic measures of fitness after stroke. In addition, sub-maximal aerobic exercise training for 6 weeks was found to decrease fatigue level in people with chronic fatigue syndrome (CFS),[135] which may attribute to the increased levels of endorphins and serotonin as the result of exercise. Other non-pharmacological may include social activities, meditation,[162] music therapy.[163] Nevertheless, these alternative treatments may not be cause-specific to PSF; and the effects in people post-stroke are yet to be established.

For people post-stroke who experience chronic fatigue (CF), alleviation of depressive symptoms appears to be a sensible practice according to the findings of this body of work. Early diagnosis of post-stroke depression (PSD) and treatment may have a positive effect not only on depressive symptoms but also on the rehabilitation outcome of people post-stroke.[164] Clinical trials revealed that only a small fraction of people with PSD were diagnosed, and fewer were treated.[13] Pharmacological intervention treatment such as fluoxetine for 12 weeks during the first 6 months post-stroke has been shown to significantly increase the survival rate.[165] Jorge and colleagues assessed the efficacy of a 12-week antidepressant treatment (fluoxetine, nortriptyline, or placebo) in 104 people post-stroke in the acute recovery phase and found significant different difference in survival rate between treatment and placebo groups. Of 53 subjects who were given full-dose antidepressants, 36 (67.9%) were alive at follow-up, compared with only 10 (35.7%) of 28 subjects who were treated with placebos. The authors concluded that treatment with fluoxetine or nortriptyline for 12 weeks during the first 6 months post-stroke significantly increased the survival of both depressed and nondepressed patients. This finding provided a feasible pharmacological interventions for people who have CF as their main fatigue complaint.

Depression and Fatigue

Although the pathophysiology of post-stroke depression is still debated, researchers have proposed various hypotheses from biological[138] and psychosocial perspectives.[137] It is unclear whether there's a causal relationship between depression and fatigue; it is also unclear whether depression should be considered as a symptom of fatigue or vice versa. We acknowledge the possible role reversal of these 2 closely related variables. Although there's no solid evidence to suggest one way or another, the close relationship between depression and fatigue cannot be neglected. Regardless the possible causal relationship between depression and fatigue and its influence on our fatigue model, the authors concluded that treatment effort should be made to focus on depression intervention, whether pharmacological or not.

5.5 Future Directions

The primary purpose of the present body work was to obtain a better understanding of PSF by characterizing the nature of different types of fatigue in people with chronic stroke. The results of this work demonstrated that aerobic fitness is an independent predictor of exertion fatigue in people post-stroke; while depression is a strong contributor of chronic fatigue.

This project established the groundwork for PSF classification and contributing factor identification. The short-term goal of this research is to continue characterizing the nature of PSF by expanding investigation in order to capture additional potential contributing factors; while the long-term goal is to develop therapeutic countermeasures and evaluate its efficacy via intervention studies in people post-stroke.

Exertion Fatigue Validation

In order to validate our EF model and confirm EF as a valid measure of fatigue, future work could control for fitness level and test individual at different levels of exercise intensity or different times of day. It is out stipulation that although subjects posses same or similar fitness level, levels of fatigue may vary.

Exercise Intervention

To the author's best knowledge, no studies have yet to develop a sound therapeutic exercise intervention program and evaluate its efficacy in people post-stroke with fatigue complaints. Previous research has shown that people post-stroke can benefit from aerobic exercise training to achieve a healthier lifestyle.[10, 77, 78, 84] It has also been established that sub-maximal aerobic exercise training for 6 weeks appeared to decrease fatigue level in people with chronic fatigue syndrome (CFS).[135] The same exercise regiment may be considered in training people post-stroke.

In addition, the effectiveness of exercise on depression has also been well documented.[166-168] Mead and colleagues conducted a review study to determine the effectiveness of exercise in the treatment of depression.[167] They found that exercise seems to improve depressive symptoms in people with a diagnosis of depression. However, the effect of exercise was not significantly different from that of cognitive therapy. Depression is commonly treated with antidepressants and/or psychotherapy, but some may prefer alternative approaches such as exercise.

Exploration of Other Potential Variables

Pain - Although it has been suggested that pain is one of the potential contributing factor to PSF,[20] like fatigue, pain is a commonly overlooked issue in people post-stroke.[71] Literature has shown that pain and severity of fatigue are strongly correlated in people who received cancer treatment.[160] However, the relationship between pain and fatigue and its possible role in the underlying mechanisms (e.g. biomarkers respond to elevated pain and stress level) in people post-stroke is inadequately studied.[70, 71] The potential impact of pain on fatigue and rehabilitation cannot be neglected in people post-stroke, especially when studying PSF. Future studies should consider investigating pain as a potential contributing factor to PSF using both quantitative (e.g. pain visual analog scale) and qualitative (e.g. case study) design. Investigators could consider 1) examining the relationship between fatigue level, pain, and quality of life, and 2) adding pain as a variable to validate the fatigue models in people post-stroke. In addition, case study with thorough documentation of daily pain level may be valuable in conjunction with quality of life assessment.

Biomarkers - Any fluid or electrolyte imbalance can potentially influence neurotransmission and muscle force and result in fatigue.[32] Payne and colleagues have identified melatonin as a possible biomarker to explain fatigue mechanisms in women with breast cancer.[149] Elevated daytime melatonin levels were observed during chemotherapy and attributed to elevated fatigue level experienced by subjects. In addition, cortisol has been identified as the primary marker of the HPA axis that may alleviate fatigue and stress.[151] Although these studies were conducted in cancer patients, the authors suggested the implication of conceptual framework in other clinical population with fatigue issues.[32] These biomarkers may provide valuable physiologic evidence and may explain the underlying mechanisms of PSF. Future study may consider examining the effect of exercise intervention on biomarkers such as serotonin, melatonin, serum bilirubin, hemoglobin counts, and lactic acid accumulation.

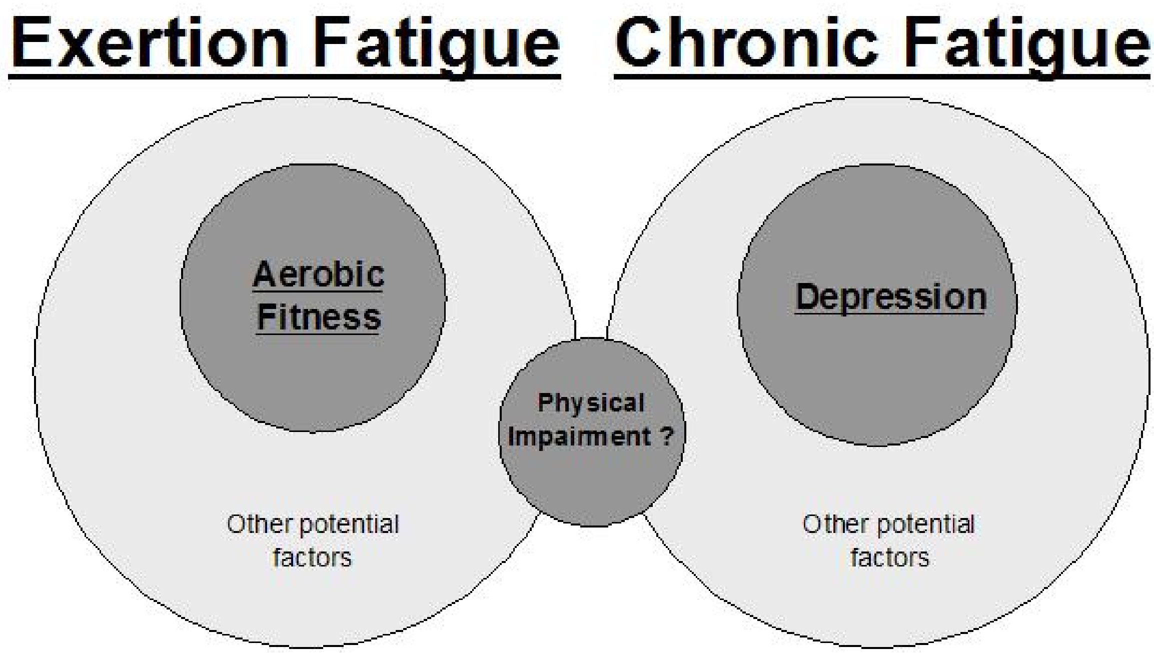
Circadian Fatigue - Although the contributing factors of circadian fatigue is still undetermined, the Visual Analog Fatigue Scale (VAFS) developed in this body of work can be used to detect real-time fatigue at different time points during the day, which provides a feasible outcome measure to investigate circadian fatigue. In addition, it has established that serotonin and melatonin are important regulators of the 24-hour sleep and wake cycles also known as the circadian cycle.[153] An individual's natural wake and sleep cycle corresponds with melatonin production, which is sensitive to light intensity. More specifically, melatonin secretion is inhibited by light and promoted by darkness.[153] The dysregulation of melatonin may affect sleep and circadian rhythms, which can result in daytime fatigue.[169] In addition, serotonin and is a precursor to melatonin and may be an indicator of depression.[51] Therefore, biomarkers such as serotonin and melatonin may offer a physiologic approach to study circadian fatigue. Future study may consider examining the relationship between the level of circadian fatigue (measured by the VAFS) and the level of melatonin counts in people post-stroke.

5.6 **Conclusions**

The work presented in this dissertation provides a snap-shot into a grander picture of post-stroke fatigue. The present findings suggest that aerobic fitness mainly contributes to exertion fatigue; while depression contributes chronic fatigue in people post-stroke. There is little doubt that PSF consists of different constructs; each construct has its own contributing factors, and these contributing factors may or may not overlap as suggested in the parallel fatigue model shown in Figure 5.1.

Our findings also suggest that rehabilitation professional should consider multiple possible contributors to a patient's fatigue after stroke; and the treatment strategies should include classification of fatigue subtype, identification of potential contributing factor, and implementation of cause-specific therapeutic treatment, whether pharmacological or not. Clinically, this is important for the rehabilitation of those with PSF complaints because clinicians may be able to treat people post-stroke with better prognosis by overcoming some of the offsetting factors. Finally, possible future studies such as those outlined previously will require validation of empirical data. If a thorough understanding of post-stroke fatigue can be obtained (i.e. all contributing factors and related mechanisms), health professions may be able to achieve optimal rehabilitative potential.

Figure 5.1. Illustration of exertion fatigue and chronic fatigue parallel models.



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Appendix I

Definitions of Fatigue Glossary

- Acute Fatigue – Fatigue with rapid onset and quicker recovery rate. Acute fatigue is considered interchangeable with exertion fatigue.

- Exertion Fatigue – A state of general tiredness that is the result of over-exertion and can be recovered by rest. Exertion fatigue is normative and is caused by extensive activities throughout daily living, with a rapid onset and shorter duration. Exertion fatigue is considered interchangeable with acute fatigue.

- Chronic Fatigue – A state of weariness unrelated to previous exertion levels that is associated with prolonged stress or pathologies. Opposite from acute or exertion fatigue, chronic fatigue has a gradual onset and longer duration.

- Circadian Fatigue – Fatigue that corresponds to the 24-hour sleep and wake cycles also known as the circadian cycle. It is generally experienced towards the end of a day's activities and can be exacerbated by sleep deprivation.

- Baseline Fatigue – Fatigue that persists prior to any physical exertion that is possibly related to circadian or chronic fatigue. Due to the design of this study, we were unable to validate the nature of this type of fatigue or to distinguish it from chronic or circadian fatigue.

Appendix II

Fatigue Severity Scale (FSS)

Subject ID: ____________

The following 9 statements refer to how you usually feel. Please read each statement and circle a number from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement.

	Strongly Disagree						Strongly Agree
During the past week, I have found that:							
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents me from sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Mean Score ________

Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol.* 1989;46:1121-1123.

Appendix III

Geriatric Depression Scale

Patient______________________ Examiner____________________________ Date___________

1. Are you basically satisfied with your life?	yes no
2. Have you dropped many of your activities and interests?	yes no
3. Do you feel that your life is empty?	yes no
4. Do you often get bored?	yes no
5. Are you hopeful about the future?	yes no
6. Are you bothered by thoughts you can t get out of your head?	yes no
7. Are you in good spirits most of the time?	yes no
8. Are you afraid that something bad is going to happen to you?	yes no
9. Do you feel happy most of the time?	yes no
10. Do you often feel helpless?	yes no
11. Do you often get restless and fidgety?	yes no
12. Do you prefer to stay at home rather than go out and do things?	yes no
13. Do you frequently worry about the future?	yes no
14. Do you feel you have more problems with memory than most?	yes no
15. Do you think it is wonderful to be alive now?	yes no
16. Do you feel downhearted and blue?	yes no
17. Do you feel pretty worthless the way you are now?	yes no
18. Do you worry a lot about the past?	yes no
19. Do you find life very exciting?	yes no
20. Is it hard for you to get started on new projects?	yes no
21. Do you feel full of energy?	yes no
22. Do you feel that your situation is hopeless?	yes no
23. Do you think that most people are better off than you are?	yes no
24. Do you frequently get upset over little things?	yes no
25. Do you frequently feel like crying?	yes no
26. Do you have trouble concentrating?	yes no
27. Do you enjoy getting up in the morning?	yes no
28. Do you prefer to avoid social occasions?	yes no
29. Is it easy for you to make decisions?	yes no
30. Is your mind as clear as it used to be?	yes no